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National Institutes of Health: Intramural and Extramural Support for Research on Sex Differences, 2000-2003

Viviana R. Simon, Tajrina Hai, Sarah K. Williams, Erica Adams, Kristen Ricchetti, and Sherry A. Marts. Society for Women's Health Research, Washington, D.C.

For more information about this study, please contact:

Viviana Simon, Ph.D.
Director, Scientific Programs
Society for Women's Health Research
Email: viviana@womenshealthresearch.org

ABSTRACT: To determine the percentage of National Institutes of Health (NIH) grants awarded for the study of biological differences between males and females, the authors carefully reviewed abstracts from successful grant applications for four consecutive years. These abstracts are publicly available on the Computer Retrieval of Information on Scientific Projects (CRISP) Database. Some institutes, such as the National Institute on Drug Abuse (NIDA), are interested and supportive of hypothesis driven research designed to study both sexes for the purposes of understanding the similarities and differences and have mechanisms in place to foster such research. However, grants awarded for the study of sex differences represent a very small percentage of the total number of grants awarded. Surprisingly, it is the institutes with the largest budgets that appear to be supporting very little or no research on sex differences.

INTRODUCTION

Women Are Not Small Men

Until the 1990's, biomedical research was firmly rooted in the male model – the belief that male biology (outside of the reproductive system) was representative of the species, and that where female biology differed from male biology it was "atypical" or "anomalous." The lack of inclusion of women in clinical research studies arose from the male model and from policies and practices that sought to protect the fetus from harm should a study participant become pregnant. This led to a lack of knowledge about female biology, and in 1985 a report from the U.S. Public Health Service concluded that this compromised the health of women (USPHS, 1985). The Society for Women's Health Research (the Society) was founded in 1990 to address these inequities in biomedical research in the U.S.

A series of advocacy efforts by the Society and other women's health activists in the early 1990s prompted the National Institutes of Health (NIH) to change its policy on inclusion of women in clinical research in 1986 (Keitt, 2003). This policy was further revised in 1993 following passage of the NIH Revitalization Act, which requires the inclusion of women and minorities as subjects in clinical research unless there is appropriate justification for not doing so (NIH, 1993).

As a result of these policy changes, evidence has accumulated of biological sex differences that have an impact on health. Biological differences between men and women result from a combination of genetic, hormonal, physiological and environmental factors. These differences begin at the time of fertilization, depending on whether an egg is fertilized with a sperm carrying an X or a Y chromosome. Gonadal hormones have organizational and activational effects during development, and to a large extent these effects influence physiology and behavior throughout the lifespan. Many sex differences are already present at birth, whereas others develop later in life (Breedlove, 1994; Coffey et al., 1998; Hindmarsh et al., 2002; Martin, 2000).

Sex differences in disease susceptibility, prevalence, time of onset and severity are evident in cancer, obesity, coronary heart disease, autoimmune disorders, mental health disorders, and others (Danielsson et al., 2001; de Perrot et al., 2000; Demirovic et al., 1995; Farzadegan et al., 1998; Holroyd-Leduc et al., 2000; Ott, 1999; Verthelyi, 2001; Whitacre, 2001; Young, 1998). Physiological and hormonal fluctuations may also play a role in the rate of drug metabolism and effectiveness of response in females and males (Anthony and Berg, 2002; Harris et al., 1995; Kashuba and Nafziger, 1998; Schwartz, 2003).

Sex Matters: The Need to Conduct Research Differently

Much of what is known about sex differences is the result of observational studies or is descriptive evidence from studies that were not designed to obtain a careful comparison between females and males (Wizemann and Pardue, 2001). The Society has long recognized that inclusion of women in study populations by itself was insufficient to address the inequities in our knowledge of human biology and medicine, and that only by the careful study of sex differences at all levels, from genes to behavior, would science achieve the goal of optimal health care for both men and women. This has given rise to a new field of scientific inquiry committed to identifying the biological and physiological differences between men and women.

In the mid-1990s, the Society instigated and raised the funds for the work of the Institute of Medicine (IOM) Committee on Understanding the Biology of Sex and Gender Differences. In 2001 this committee published its findings in a landmark report entitled *Exploring the Biological Contributions to Human Health: Does Sex Matter?* (Wizemann and Pardue, 2001). This report emphasizes the need for hypothesis-driven research on sex-based differences at the molecular, cellular and whole organism levels and at different stages of the life span. The committee found that the research literature contains few data on the effects of the sex chromosome complement (XX or XY) at the cellular level, and that animal models mirroring human sex differences need to be developed. A recent study shows that females express significantly more genes than males, since approximately 15% of the genes in their second X-chromosome fail to be inactivated (Carrel and Willard, 2005). Therefore, research on sex differences needs to occur in basic science laboratories by identifying the chromosomal sex of cell lines, using both male and female animals, and including men and women as research subjects in all phases of clinical research, including drug and device development.

The IOM committee also noted that incorrect use of the term "gender" as a euphemism for "sex" is a barrier to progress in research on sex differences. The committee offered these definitions: "The committee defines *sex* as the classification of living things, generally as male or female according to their reproductive organs and functions assigned by the chromosomal complement, and *gender* as a person's self-representation as male or female, or how that person is responded to by social institutions on the basis of the individual's gender presentation." (Wizemann and Pardue, 2001).

Sex Differences Research at the National Institutes of Health

The NIH is the primary source of federal support for independent investigator-initiated biomedical research in the U.S. The influence of the NIH extends beyond its direct impact on research, as many private biomedical research funders model their grant programs after those at the NIH.

A U.S. General Accounting Office (GAO) report published in 2000 concluded that although "NIH has made significant progress in implementing a strengthened policy on including women in clinical research . . . NIH has made less progress in implementing the requirement that certain clinical trials be designed and carried out to permit valid analysis by sex, which could reveal whether interventions affect women and men differently" (GAO, 2000). Moreover, the GAO found that NIH had no mechanisms in place to determine the degree to which the NIH supports sex differences research.

In addition to external reports by the GAO and IOM that signaled the need for more progress on sex differences research, there have developments internal to NIH to spur advances in this area. In addition to the 1993 revitalization act, the NIH convened in 2001 at the Society's urging the "Working Group of Representative Scientific Journal Editors of the Advisory Committee on Research on Women's Health," to discuss the importance of publishing sex and gender analyses of research data. The working group developed principles for the publication of clinical research results including: clinical studies should be analyzed to see if there is an effect of sex and if there is no effect, it should

be so stated in the results; and statistical limitations of the analysis should be made clear.

The current report examines whether the growing body of literature on sex differences, external reports about NIH practices and internal efforts to promote this type of research are reflected in increased levels of NIH support for research on sex differences. In light of these reports and events, we hypothesized, there should be indications of a larger number of NIH-sponsored research projects in basic and clinical sciences involving sex differences since 2001.

METHODS

In 2003, Society staff undertook a review of the publicly available information in the Computer Retrieval of Information on Scientific Projects (CRISP) Database to determine what proportion of extramural and intramural grants funded by the Institutes and Centers (I/Cs) of the NIH include an examination of sex differences as at least one of the specific aims. The CRISP database is maintained by the NIH Office of Extramural Research and contains the abstracts of all grant applications funded by the NIH, including intramural and extramural grants, fellowships, career awards, clinical research center grants, program project centers, contracts and cooperative agreements. We searched for proposals that included an investigation of sex differences in the research hypothesis or the project specific aims. We examined results from the years 2000 through 2003, the year before and two years after the release of the IOM report. We used these data to determine the level of support for sex differences research provided by each NIH I/C over this period.

Search Strategy

The terms "sex" and "gender" are often used interchangeably in the literature and in grant proposal applications; therefore, both terms were used to query the CRISP database. A stem[1] query was conducted using the phrase *sex differences*, including all types of investigator-initiated grant awards (new, competing and non-competing), all activities (R, P, K, F awards, etc,), all internal review groups (IRGs), and all NIH I/Cs from 2000 through 2003. The query [$(sex differences)] provided 448 hits. A stem query performed with the phrase *gender differences*, [$(gender differences)] resulted in 5463 hits. The search did not include contracts or cooperative agreements. The results of both searches were combined and duplicates were eliminated before further analysis was performed.

Data Collection and Analysis

The abstracts obtained from both queries were read in full and evaluated to identify only those studies that included male and female subjects, that were hypothesis-driven, and that included at least one specific aim intended to compare female and male subjects to understand any sex differences (including model organisms and human studies). Abstracts were excluded from the final analysis if one or more of the following were true:

1) The abstract did not specifically mention comparison of male and female subjects.

2) The study included only female or only male subjects.

3) Gender was mentioned only as a stratification category of the investigation among others such as ethnicity, age and socio-economic status, such that sex or gender differences were not part of the study hypothesis.

4) The study was on a disorder that solely affects one sex, such as prostate cancer or ovarian cancer.

For purposes of further analysis, the following project data were recorded: year, institute, species and terminology used (i.e., "sex" or "gender").

Once all abstracts were read, analyzed and coded, the percentage of grants for studies of sex/gender differences awarded by each institute was calculated from the total numbers of grants awarded by that institute each of the years from 2000 - 2003. Throughout this paper, the numbers presented are percentages of total grants awarded per year by the NIH as a whole or by individual I/Cs. The number of grants awarded rather than the dollar amount awarded was used in the analysis to compensate for the large variation in the size of I/C budgets. Also, the dollar amounts of individual grants are not disclosed in the CRISP database.

Data for a total of 19 I/Cs are presented here. One institute and seven centers awarded no grants for the study of sex or gender differences; therefore, these were not included in the final analysis. These were: the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the National Center for Complementary and Alternative Medicine (NCCAM), the National Center on Minority Health and Health Disparities (NCMHD), the Fogarty International Center (FIC), the National Library of Medicine (NLM), the Center for Information Technology (CIT), and the Center for Scientific Review (CSR).

[1] A stem search expands the list of words to include all words having the same stem or root. (e.g. carcinogen expands to search for projects including carcinogen, carcinogenic, carcinoma, carcinomas, and carcinogenesis.)

Request for Applications and Program Announcements

To determine if the percentage of grant awards that address sex differences correlates with the extent to which I/Cs expressed interest in such research, we collected information on Requests for Applications (RFAs) and Program Announcements (PAs) released between 1999 and 2003 that called for proposals for research on sex differences. We searched the *NIH Guide to Grants and Contracts* and individual I/C websites for such announcements distributed by the six I/Cs with the largest percentages of funded grants on sex differences.

RESULTS

Results for All NIH I/Cs

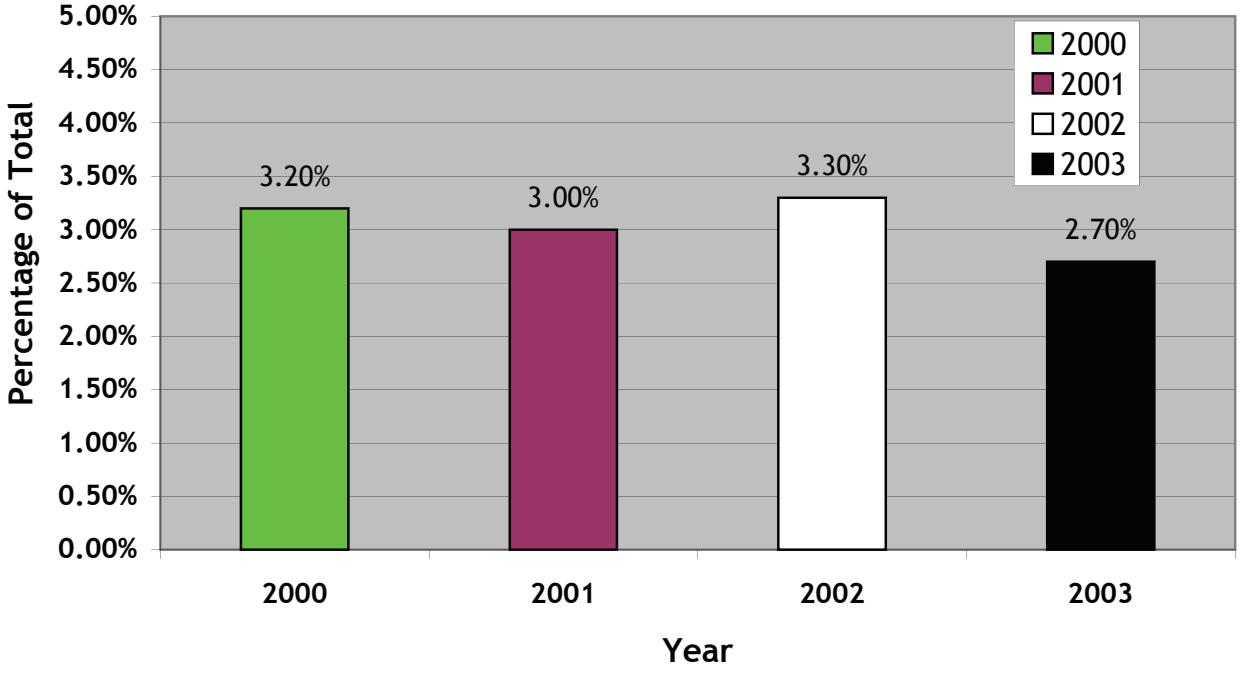
Table 1 lists the number of grants obtained with the original search, which included all NIH I/Cs and all types of grants including but not limited to: research, fellowships, training and career development per year. These data are shown graphically in Figure 1.

During the years 2000 to 2003, the average yearly percentage of grants awarded for the study of sex/gender differences was 3% of the total number of grants awarded NIH-wide. Although during this time period the number of total grants awarded increased by nearly 20%, the number of grants awarded that included sex/gender differences did not follow this same trend. In fact, compared to 2000, where 3.2% of the awarded grants included studies of sex/gender differences, in 2003, only 2.7% of the grants included such studies. This decreasing trend represents a nearly 16% reduction in sex/gender differences grants funded in 2003 compared to 2000. Although the percentage of sex/gender differences grants increased in 2002, compared to the two previous years, that increase was not maintained.

Table 1. Number of grants identified using the query "sex differences" and "gender differences" awarded by all NIH institutes from 2000 - 2003

Year	**$(sex differences)**	**$(gender differences)**	Combined per year	Total number of grants awarded	Percentage of total NIH grants on sex/gender differences
2000	128	1297	1425	44,392	3.2 %
2001	94	1324	1418	46,845	3.0 %
2002	114	1527	1641	49,716	3.3 %
2003	112	1315	1427	53,000	2.7%
2000-2003	***448***	***5463***	***5911***	***193,953***	***Average = 3.0%***

Figure 1. Percentage of NIH-wide grants obtained by queries on "sex differences" and "gender differences"



Results for Individual I/Cs

The percentage of grants awarded by individual I/Cs over the period of 2000-2003 that included analysis of sex differences is shown in Figure 2. The maximum percentage of grants funded for the study of sex/gender differences did not exceed 8% of total awards for any one I/C. Over these four years, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) had the highest percentage; 7.91% of NIAAA grant awards included an investigation of sex/gender biological differences. The National Institute on Drug Abuse (NIDA) had the second largest percentage (5.27%), followed by the National Institute of Nursing Research (NINR, 5.27%), the National Center for Research Resources (NCRR, 4.96%), the National Institute of Aging (NIA, 4.46%), and the National Institutes of Mental Health (NIMH, 3.68%). (Figure 2)

Figure 2. Percentage of total grants awarded for the study of sex/gender differences from 2000-2003

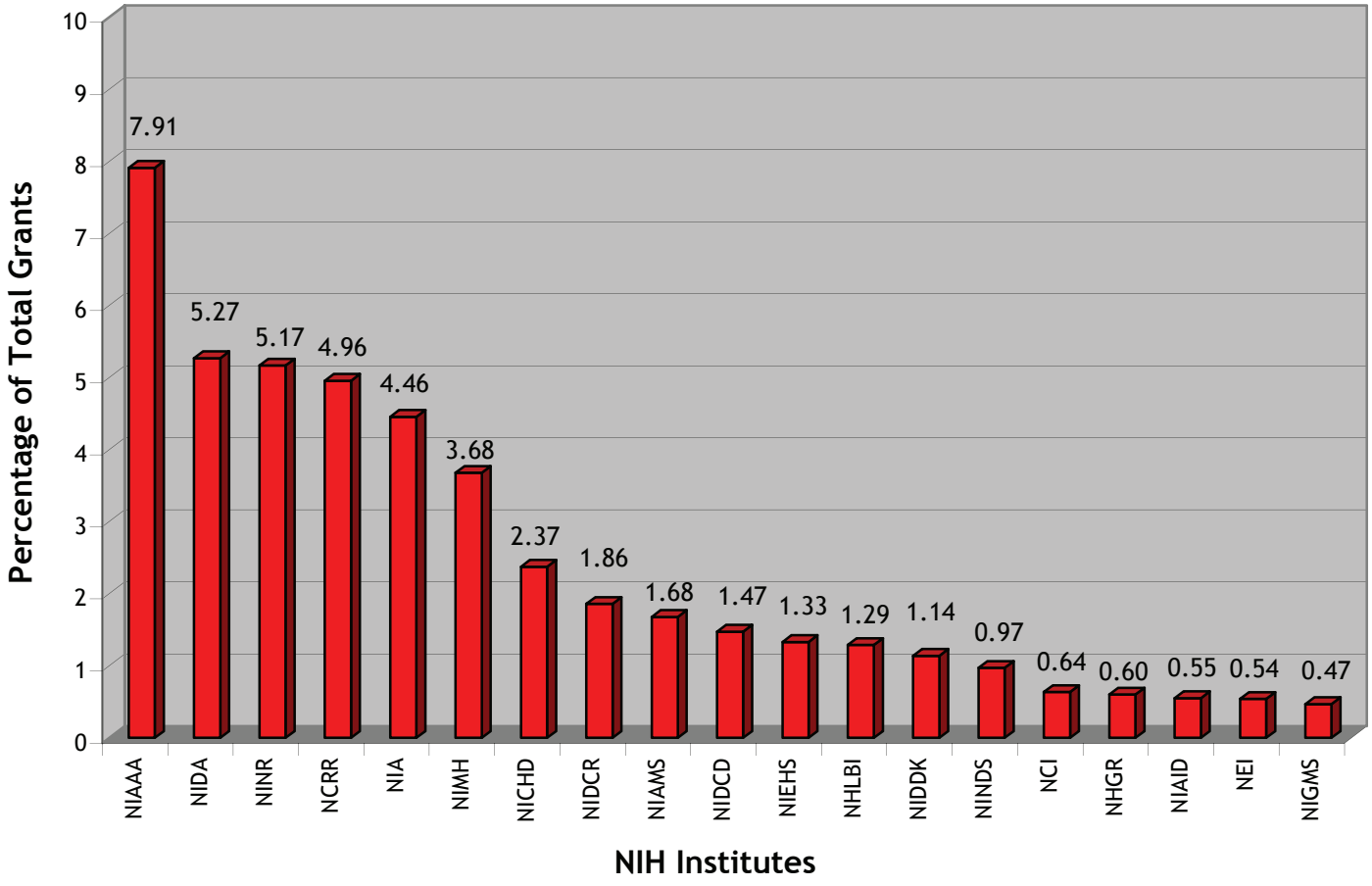


Figure 3 shows changes in that percentage for the I/Cs that had the highest proportion of sex/gender-based studies throughout the period studied. With the exception of the NIMH, where the percentage remained nearly constant throughout 2000 – 2003, most of the other institutes showed a decrease of 1.5% - 2.0% in the proportion of grant awards that included a sex/gender comparison.

Some institutes showed modest increases from 2000-2003 in percentage of awards made that included the study of sex or gender differences. Among these are National Institute of Child Health and Human Development (NICHD), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Environmental Health Sciences (NIEHS), National Institutes of Diabetes & Digestive & Kidney Diseases (NIDDK) and National Institutes of Allergies and Infectious Diseases (NIAID). (Figure 4) However, none of these institutes had more than 3% of their grants supporting sex or gender differences research.

Figure 3. Percentage of grants for research on sex/gender differences: institutes and centers with the largest proportion of grants in this area, 2000-2003

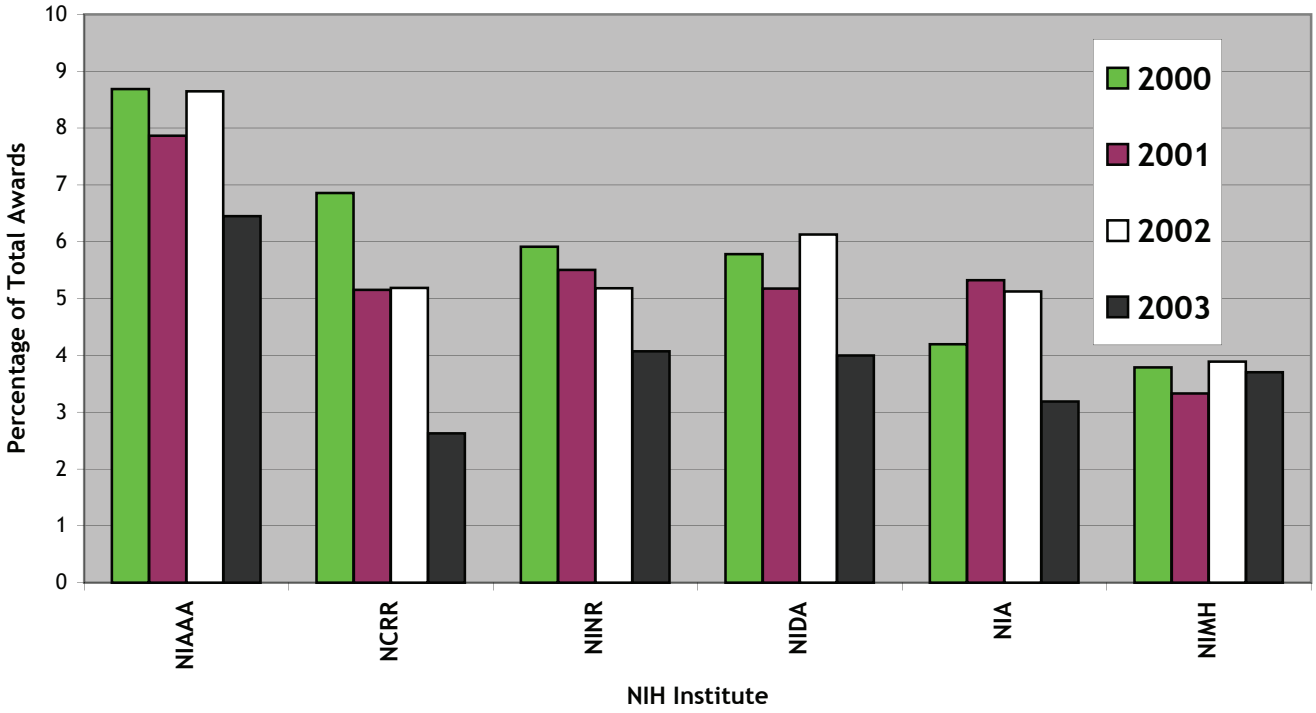


Figure 4. Institutes that show modest increases in the percentage of grants awarded for research on sex/gender differences from 2000-2003

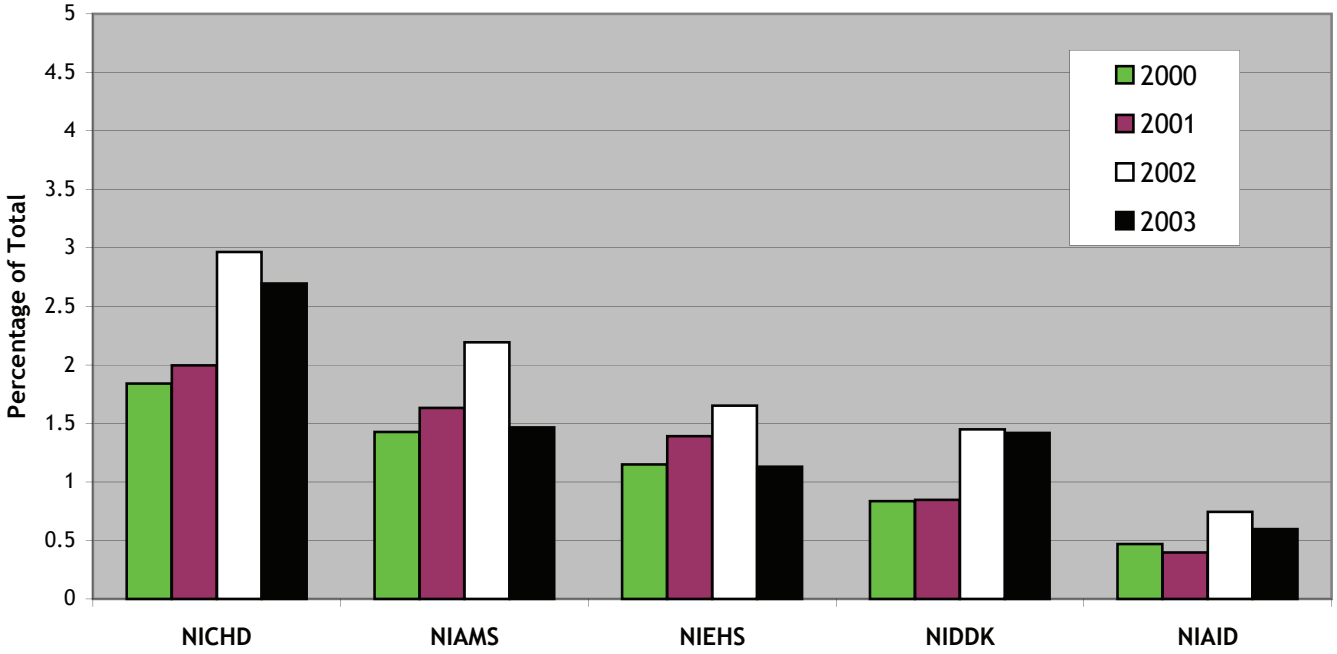


Table 2: Number of grants awarded by NIH institutes and centers, 2000-2003

NIH Institute	Number of Grants Awarded Between 2000-2003	Percentage of Grants for the Study of Sex/Gender Differences	Rank Order by Percentage of Grants on Sex Differences
NCI	6496	0.63	15
NHLBI	5485	1.28	12
NIGMS	5298	0.47	19
NIAID	4580	0.56	17
NIDDK	3899	1.15	13
NINDS	3369	0.96	14
NIMH	**3330**	**3.68**	**6**
NICHD	2519	2.4	7
NIDA	**1977**	**5.24**	**2**
NIA	**1750**	**4.44**	**5**
NEI	1534	0.54	18
NIAMS	1291	1.68	9
NIDCD	1089	1.47	10
NIAAA	**942**	**7.88**	**1**
NIEHS	936.5	1.33	11
NCRR	**889.25**	**4.67**	**4**
NIDCR	829.25	1.84	8
NINR	**438.75**	**5.13**	**3**
NHGRI	257.75	0.58	16

The NIH institutes that fund the largest number of grants award a smaller percentage of those grants for the study of sex and gender differences (Table 2). For example, the three institutes that funded the largest number of grants during this period, National Cancer Institute (NCI), National Heart Lung and Blood Institute (NHLBI), and the National Institute of General Medical Sciences (NIGMS), ranked respectively 15th, 12th and 19th out of the 19 I/Cs analyzed in the proportion of those grants that addressed sex differences.

RFAs and PAs for research involving human subjects issued since the year 2000 include standard language that calls for the inclusion of women and minorities in clinical trials, and for analysis of the data by subgroup and subpopulation. We found that very few RFAs released between 2000 and 2003 included any additional language calling for analysis of the results by sex, even in cases where prior research has shown that sex differences exist.

Our search of RFAs and PAs issued for grants awarded in 2000-2003 found that the National Institute on Drug Abuse (NIDA), which had the second highest percentage of grants studying sex differences, has many more RFAs and PAs focused on sex differences than any other I/C. NIDA is unique in that the Institute has established the Women and Gender Differences Research (W&GR) workgroup, comprising representatives from all branches and program divisions, to promote sex and gender difference research within NIDA. Moreover, NIDA has consistently issued PAs that focus on women and gender in various topics ranging from prescription drug abuse to the molecular genetics of drug addiction.

DISCUSSION

The IOM Committee on Understanding the Biology of Sex and Gender Differences said "the study of sex differences is evolving into a mature science. . . . The next step is to move from the descriptive to the experimental phase and establish the conditions that must be in place to facilitate and encourage the scientific study of the mechanimsms and origins of sex differences." (Wizemann and Pardue, 2001) Among these conditions is the recognition and support of sex differences research by the NIH and other major funding agencies.

The analysis presented here is limited to the information publicly available in the CRISP database that was provided by investigators at the time of submission of their grant application. It is likely that the data provide a close approximation of the degree to which NIH extramural funding supports research on sex and gender differences; however, the information in the CRISP database does not provide any insight as to whether the research was actually performed as it was proposed on the grant application.

Grants for studies of only one sex were excluded from this analysis, because we were specifically looking for studies that included the study of sex or gender differences as part of the individual study design. Although the results of single-sex studies may be compared to look for a sex difference, and may drive the planning and design of future studies of sex differences, such comparisons do not constitute the targeted, hypothesis driven research that we believe will move this research area forward.

Our results show that, for the most part, the NIH institutes with the largest budgets, and hence the most impact on the conduct of biomedical research in the U.S., have provided relatively little support for sex differences research in their areas. This is despite the fact that there is evidence for sex differences in the systems or conditions under study by these institutes. The three institutes with the largest extramural research budgets, the NCI, NHBLI and the NIAID, represent disease areas and physiological systems for which there is ample evidence for significant sex differences. However, over the four years covered by this study, the proportion of grant awards that supported research on sex differences in these institutes was 0.6%, 1.3%, and 0.6%, respectively. These proportions are well below the total-NIH average of 3%.

It would be expected that known sex differences in the prevalence and incidence of the diseases and conditions under study at each institute would contribute to disparities in the proportion of research on sex differences. However, this did not seem consistently to be the case. Three of the six institutes that had the largest proportion of grants for sex differences research, NIAAA, NIDA and NIMH, address mental health and behavioral issues. As a result, research on sex differences in areas such as biological basis of addiction, post-traumatic stress disorder, and depression has advanced significantly in the recent past. In contrast, of the eight institutes with the lowest percentage of grants for sex and gender differences, at least five (NIAID, NCI, NINDS, NIDDK, and NHLBI) include in their mission statements, focus on conditions (STDs, heart disease, stroke, diabetes, lung cancer, melanoma) and biological systems (cardiovascular, pulmonary, gastrointestinal, nervous, and endocrine) that are known to exhibit significant sex differences. Two NIH institutes represent research areas where the demographics of the populations under study are predominately female: the National Institute on Aging (NIA), and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). Of these two institutes, NIA was among the top five institutes for funding of sex differences research, with nearly 4.4% of grants over the four-year period funding this type of research. In contrast, less than 1.7% of the grants funded by NIAMS during this period addressed sex differences. Because of its focus on reproductive health, we expected the National Institute of Child Health and Human Development (NICHD) to have a larger proportion of single-sex studies and a relatively small proportion of its grants addressing sex differences. However, NICHD had the seventh highest proportion of sex differences grants, 2.4%.

Two of the I/Cs that had the largest proportion of grants for sex differences research were NINR and the NCRR. The NCRR grants listed in CRISP are supported as supplements to the NCRR General Clinical Research Center (M01) grants, and are intended to develop the knowledge and skills of clinical investigators (i.e., investigators who perform research on human subjects or material of human origin). The primary mission of NINR is to support research into the effective care of patients during illness and recovery, and the reduction of risk of disease and disability. It is encouraging that the two institutes whose programs emphasize research that supports clinical care demonstrate a high interest in research on sex differences.

Of the I/Cs that had no grants for sex differences research, three the National Library of Medicine (NLM), the Center for Information Technology (CIT), Center for Scientific Review (CSR) primarily perform administrative or support functions and so would not be expected to appear with our search criteria. The National Institute of Biomedical Imaging and Bioengineering (NIBIB) is the newest NIH institute, and the National Center for Minority Health and Health Disparities (NCMHD) is the newest NIH center, both established in 2000. The National Center for Complementary and Alternative Medicine (NCCAM) was established as a center with grant-making authority in 1999. We anticipate that as the grant portfolios of these three I/Cs develop, sex differences research will be included.

The Fogarty International Center (FIC) offers training and research grants for international projects, and several of its initiatives are cosponsored by the NIH Office of Research on Women's Health (ORWH). It is surprising and dismaying that none of the FIC's grantees have explicitly included studies of sex or gender differences in their research proposals.

Among the institutes with the highest proportion of grants for sex differences research, we noted a consistent drop in that proportion in 2003. This is both surprising and disappointing, given the increased awareness of health areas affected by sex differences, particularly in the fields of behavioral research and neuroscience.

RECOMMENDATIONS

Some may argue that it is too early to see meaningful increases in sex differences research funding by NIH because new research needs take many years to be actualized through grant solicitation, development, application and review processes. The IOM report, however, did not map uncharted territory; it was instead a collection and affirmation of already established scientific evidence on sex differences. This – coupled with efforts within NIH, by other governmental agencies or bodies, and advocacy organizations to promote sex differences research over the last 10-15 years – is enough to expect more progress.

At present, the NIH explicitly requires the inclusion of women and analysis by sex only for late-phase clinical studies that are large trials testing a treatment or other intervention. NIH research guidelines must be updated and modified once again to actively promote sex differences research at all levels, including basic research in cell and tissue culture, the development and study of appropriate animal models and in early stage clinical research, as called for by the IOM.

We do not recommend the creation of a separate I/C for sex differences research; such research should be a part of the portfolio of nearly all of the existing NIH I/Cs. The individual I/Cs must carefully consider ways to promote interest and progress in sex differences research among their extramural program staff, and their grantees. Among the potential strategies for accomplishing this are:

- establish an extramural program position (or, for the larger institutes, positions) responsible for reviewing RFAs and PAs to determine whether sex differences should be a focus of the announcement;
- issue RFAs and PAs that have hypothesis-driven sex differences research as the primary focus;
- offer grant supplements to investigators to add exploration of sex differences to currently funded projects; and
- track publications reporting on sex differences that result from I/C-funded research.

The issuance of an NIH-wide PA inviting applications for sex and gender differences would serve to inform the research community of the NIH's interest in and commitment to this research.

Progress in sex differences research benefits from collaboration across research disciplines and medical specialties and among all research approaches, from molecular biology to epidemiology. The importance of sex differences to health care necessitates a "bench-to-bedside" translation that requires integration of research findings from studies at the cellular level, in animals and in human subjects. Coordination of sex differences research and research resources, including the establishment and use of databases and tissue sample repositories, and the development of animal models, will be crucial as the field matures.

Sex differences research would benefit from increased trans-NIH I/C cooperation and coordination. The NIH ORWH has taken on this effort, but the limited budget of this office, coupled with its lack of direct grant-making authority limit its effectiveness. NIH faced a similar challenge in its efforts to coordinate research on HIV/AIDS, and the structure, function and authority of the NIH Office of AIDS research could serve as another model for the planning, coordination, and evaluation of sex differences research at NIH, including the setting of research priorities and a role in determining the budgets for such research.

The NIH Roadmap is the most recent attempt to foster trans-I/C research efforts. The NIH Roadmap is intended to provide "a framework of the priorities NIH as a whole must address in order to optimize its entire research portfolio. It lays out a vision for a more efficient and productive system of medical research. The NIH Roadmap identifies the most compelling opportunities in three main areas: new pathways to discovery, research teams of the future, and re-engineering the clinical research enterprise" (Health, 2004). Should the Roadmap initiatives succeed in accomplishing their aims, this would be another model to look to for fostering sex differences research through NIH extramural grant award mechanisms.

As the IOM report acknowledged, sex does matter in health and disease, throughout the entire lifespan. Failure to explore this crucial biological variable, carefully and thoroughly, will leave gaps in our knowledge of human biology and will have a significant negative impact on the health of women and men.

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