EPIDEMIOLOGY AND SOCIETY
A Forum on Epidemiology and Global Health

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Did Medical Research Routinely Exclude Women? An Examination of the Evidence

Many pesons have voiced the belief that medical research studies often excluded women. Wenger and colleagues argued, "The infrequent inclusion of women in clinical research until very recently warrants scrutiny to clarify whether women have been excluded from participation for medical reasons."[1] LaRosa and Pinn lamented, "The exclusion of some women from clincal studies may sometimes be valid, but not all women all the time."[2] A 1993 editorial in *The New England Journal of Medicine* made this categorical assertion: "There is little doubt that women have been systematically excluded as subjects for study. . .it is not surprising that most clinical trials have been heavily, if not exclusively, weighted toward men".[3]

The purpose of this commentary is to examine the empirical basis for the proposition that medical research, especially research sponsored by the National Institutes of Health (NIH), commonly excluded women. I examine both epidemiologic studies and clinical trials, analyzing both the number of studies by the sex of their participants, and sex-specific enrollments in medical research studies. I draw upon previously-published articles, analyses of the Medline database (which first became operational in 1966), and internal NIH documents.

I pay particular attention to the period before 1990. I emphasize this time frame in order to minimize the effects of the establishment of the NIH Office of Research on Women's Health in 1990, the appointment of Dr. Bernadine Healey as NIH director in 1991, and the passage of federal legislation in 1993 intended to assure female participation in NIH research.

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Participation of Women in Clinical Trials

Two articles examined the extent to which women participated in the early clinical trials. In the 1970s, the NIH published an annual listing of clinical trials in its *NIH Inventory of Clinical Trials.* Dickerson and Min analyzed all 293 NIH trials funded in 1979, excluding trials sponsored by the National Cancer Institute. A review of the 293 studies revealed that 268 trials included both men and women, representing 91% of the total.[4] Of the remaining 25 studies, 12 were male-only and 13 were female-only. Thus, women participated in 96% of clinical trials.

Meinert and colleagues reviewed and tabulated clinical trials published in five leading medical journals: *Annals of Internal Medicine, British Medical Journal, JAMA, The Lancet,* and *New England Journal of Medicine.*[5] Among the 115 trials published in 1985, men represented 11.0% and women represented 89.0% of all enrollees (Table 1). In 1990 and 1995, male enrollment was recorded at 38.5% and 52.6%, respectively. The large number of female-only trials on neoplasms largely explained the preponderance of women in the 1985 and 1990 trials.

These analyses indicate that before 1990, women routinely participated in clinical trials, and in numbers that are more than proportionate to the number of women in the overall population. Although these analyses of clinical trials appear to be persuasive, they leave unanswered the question of female participation in epidemiologic research.

Participation of Women in Epidemiological Research

No broad-based analysis has been accomplished to date of female participation in epidemiologic research. To examine this issue, I undertook a Medline database search. All studies cataloged in Medline are coded by a number of variables, including condition, year, type of study, and sex of the study participants.

TABLE 1. Sex-Specific Enrollment in Clinical Trials, 1985, 1990, and 1995

	Number of Trials	Males		Females	
		Number	Percent	Number	Percent
1985	115	21,878	11.0	177,130	89.0
1990	227	104,356	38.5	166,545	61.5
1995	261	229,390	52.6	207,068	47.4
Total	603	355,624	39.2	550,743	60.8

Adapted from Meinert CL, et al. Gender representation in trials (Table 3). Control Clin Trials 2000; 21: 462–475

It is likely that some of the articles represented duplicate reports on the same research project, but this effect could not be controlled.

The search used the descriptors "Epidemiology," "United States," and "Human." We analyzed 12 conditions that represent the leading causes of death in the United States and other major areas of research at the NIH.

Table 2 displays the number of sex-specific "hits" for the number of studies published for each of these 12 conditions during the period 1966–1990. During this time frame, 13,119 of the published epidemiologic studies included men, and 15,193 studies included women. These numbers represent a 15.8% difference favoring women. Note that most of these studies included *both* males and females, and these studies are counted in both columns.

A similar number of studies on arthritis, flu, and mental health included men and women. In the areas of AIDS, chronic obstructive pulmonary disease (COPD), heart disease, injuries, and stroke, more epidemiologic studies included men. In the areas of cancer and diabetes more studies included women. In epidemiologic studies on reproduction and sex hormones, the difference is pronounced.

Medline Analysis of Female Participation in Clinical Trials

To elaborate upon the above findings, I conducted a Medline analysis of the same conditions as those listed in Table 2, substituting the "clinical trial" Publication Type instead of "epidemiology" as a general search term. All other search terms were identical to those for the first Medline search.

Table 3 reveals interesting similarities and contrasts to the first search. A similar number of clinical trials on arthritis, COPD, injuries, mental health, and stroke included men and women. In the areas of AIDS, diabetes mellitus, heart disease, and flu, more trials included men. And in the areas of cancer, reproduction, and sex hormones, more studies included women. Overall, the total number of clinical trials favored women by a 26.5% margin, an even greater disparity than that noted for the Medline analysis of epidemiologic studies.

The findings on cancer research are buttressed by two analyses of participants in cancer trials. One study of 1989 enrollees in the National Cancer Institute (NCI) Clinical Trials Cooperative Group Program reported 43% male and 57% female participation.[6] The analysis reported almost 40 clinical trials for breast cancer, compared with 10 trials for prostate cancer. A more recent report from the Southwest Oncology Group revealed that 42% of study enrollees for the 1993–1996 period were male, and 58% female.[7]

Many of the early claims of sex bias centered around cardiovascular disease research.[1] In the area of heart disease, Table 3 reveals 137 published clinical trials that included men and 78 trials that included women, nearly a two-fold difference that favors men.

But this differential must be considered in light of the fact men have long experienced almost twice the

TABLE 2. Sex-Specific Analysis of Epidemiologic Studies, 1966–1990

	Male	Female
AIDS	922	790
Arthritis	331	334
Cancer	4,650	5,059
COPD	345	294
Diabetes mellitus	790	839
Flu	175	178
Heart disease	2,226	1,741
Injuries	1,814	1,659
Mental health	356	350
Reproduction	1,068	3,405
Sex hormones	96	250
Stroke	346	294
TOTAL	13,119	15,193

COPD = chronic obstructive pulmonary disease.
Source: Medline database.

TABLE 3. Sex-Specific Analysis of Clinical Trials, 1966–1990

	Male	Female
AIDS	20	12
Arthritis	19	22
Cancer	14	194
COPD	16	15
Diabetes mellitus	25	20
Heart disease	137	78
Flu	7	4
Injuries	18	22
Mental health	29	27
Reproduction	20	139
Sex hormones	2 (Testosterone)	25 (Estrogen)
Stroke	22	19
TOTAL	456	577

COPD = chronic obstructive pulmonary disease.
Source: Medline database.

age-adjusted mortality risk of women. Also, clinical trials often prefer to recruit patients under the age of 65 to reduce confounding clinical variables. But heart disease typically develops 10–15 years later in women than men, so many potential female enrollees were not recruited into cardiovascular trials on the basis of their age.[8]

Recent Trends in Sex-Specific Enrollments

In response to the perception that medical research routinely excluded women, the U.S. Congress added provisions to the NIH Revitalization Act of 1993 which aimed to achieve equal sex participation in NIH-sponsored research. The regulations published pursuant to this Act state,

"To this end, the guidelines published here are intended to ensure that ALL future NIH-supported biomedical and behavioral research involving human subjects will be carried out in a manner sufficient to elicit information about individuals of both genders."[9]

The Act also mandated the establishment of a computerized tracking system to monitor enrollments in all NIH research studies.

In 1994, the first year in which the tracking system was operational, men were found to represent 44.9% of enrollees in extramural research, women 51.8%, and the sex of the remaining 3.3% was unknown.[10] By 1994, male participation had fallen to 32.2%.[11] Numerically, 1,501,687 fewer males than females were enrolled in NIH extramural research in 1997.

The percentage decline in male enrollments appears to be associated with the growth in female-only protocols. In 1994, the NIH sponsored 95 male-only studies, and 219 female-only studies.[12] By 1997, the disparity had widened to 244 all-male studies vs. 740 all-female studies.[13] Based on data provided by the NIH Office of External Research, the 1997 single-sex studies enrolled 85,901 males and 1,264,381 females. This difference of 1,178,480 persons accounts for much of the overall NIH shortfall in male enrollment.

Conclusion

A review of sex-specific enrollments in medical research studies, and an examination of the number of epidemiologic studies and clinical trials that included men and women, point to two conclusions: 1) Historically, women were routinely included in medical research, and 2) Women have participated in medical research in numbers at least proportionate to the overall female population.

These conclusions were foreshadowed by the Institute of Medicine's Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies, which concluded in 1994 that the committee could not "nail down the perception that women have been under represented" in clinical trials.[14]

The recent decline in male participation in NIH research has triggered expressions of concern about the underrepresentation of men in medical research.[15] Overall, men have a higher age-adjusted death rate than women for each of the top 10 leading causes of death.[16] Given these considerations, I conclude that men are currently underrepresented in NIH.

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