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Effect of Gender on the Progression of Nondiabetic Renal Disease: A Meta-Analysis

JOEL NEUGARTEN, ANJALI ACHARYA, and SHARON R. SILBIGER
Renal Division, Department of Medicine, Montefiore Medical Center and the Albert Einstein College of Medicine, Bronx, New York.

Abstract. There is previously published evidence that male gender is associated with a more rapid rate of progression of nondiabetic chronic renal disease. However, some investigators have concluded that no such association exists. To help resolve this issue, a meta-analysis was performed using 68 studies that met defined criteria and contained a total of 11,345 patients to evaluate the effect of gender on the progression of nondiabetic chronic renal disease. The results indicate that men with chronic renal disease of various etiologies show a more rapid decline in renal function with time than do women.

We have previously provided evidence that male gender is associated with a more rapid rate of progression of nondiabetic chronic renal disease (1). However, other investigators have concluded that no such association exists (2). Moreover, the results of individual studies have not universally found an adverse effect of male gender on the progression of renal disease (1). To help resolve this issue, we performed a meta-analysis using 68 studies that met defined criteria and contained a total of 11,345 patients to evaluate the effect of gender on the progression of nondiabetic chronic renal disease. The results indicate that men with chronic renal disease of various etiologies show a more rapid decline in renal function with time than do women.

Materials and Methods

Published reports examining the effect of gender on the progression of nondiabetic chronic renal disease (CRD) (mixed etiology), IgA nephropathy, idiopathic membranous nephropathy, and autosomal dominant polycystic kidney disease (ADPKD) were identified by conducting a search of articles indexed in the Medline database for the years 1975–1998. The search was conducted by: (*1*) cross-referencing the terms "glomerulonephritis," "nephritis," and "nephropathy" with "IgA," "Berger's," and "membranous;" (*2*) cross-referencing the term "gender" and the key words "sex factors" with the terms "renal" and "kidney;" and (*3*) using the key words "kidney disease" and "polycystic." Additional studies were identified through examination of the bibliography of retrieved articles. From this group, we identified those studies that specifically examined the impact of gender on renal disease progression in humans. Selection was limited to studies with 25 or more subjects followed for an average of 6 mo or longer. Unpublished abstracts and letters to the editor were not included unless they updated a previously published study. Studies written in a language other than English were not included unless identified through a bibliographic citation. Multiple publications from the same investigators were carefully examined to exclude duplication of subjects. Two investigators independently examined each retrieved study and extracted the following data: year of publication, number of male and female subjects, study design, administered treatment, statistical analysis, and outcome measure.

Meta-analyses were performed on all identified studies within each of the study categories (CRD, IgA nephropathy, membranous nephropathy, ADPKD) using a fixed-effects model. Meta-analyses were repeated after excluding those studies that failed to use one of the following outcome measures: end-stage renal disease (ESRD) requiring renal replacement therapy, change in isotopically determined GFR, or, in the case of ADPKD only, age of institution of renal replacement therapy.

Meta-analyses were conducted according to the method of Hedges and Olkin (3). Calculations were made using DSTAT 1.10 with a fixed-effects model (4). The standardized effect size estimate (d value) was calculated for each study as the difference between outcomes of men and women expressed as SD units. A mean effect size and a 95% confidence interval (CI) were calculated by averaging all d values weighted by the reciprocal of their variance. The mean weighted correlation, r, was also calculated. The Q statistic was calculated as a measure of heterogeneity of effect size.

Meta-analyses were repeated using the random-effects model of DerSimonian and Laird (5). The standardized effect size estimate and Q statistic were calculated as described (5).

A meta-regression analysis was performed to delineate possible reasons for heterogeneity among the studies. Standardized effect size estimate was the dependent variable, and the following were independent variables: year of publication, total number of subjects, number of male subjects, number of female subjects, mean patient age, year of study publication, immunosuppressive therapy, minimum duration of follow-up, mean duration of follow-up, outcome measure, type of renal disease, and study quality (retrospective, prospective observational, randomized-controlled, etc).

A funnel plot was constructed of standardized effect size *versus* subject number to assess publication bias. Unequal distribution of points above and below the mean standardized effect size suggests publication bias (6).

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Correspondence to Dr. Joel Neugarten, Renal Laboratory, Montefiore Medical Center, 111 East 210 Street, Bronx, NY 10467. Phone: 718-920-4991; Fax: 718-920-6658.

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Results

Chronic Renal Disease

Eight studies, containing a total of 2229 patients, were selected for meta-analysis (7–14) (Table 1). The mean age of the patients was 48.1 ± 2.4 with a mean duration of follow-up of 62.2 ± 25.8 mo. Five other studies could not be included in the analysis because they did not report sufficient statistical data to calculate effect size (15–19). Of these excluded studies, two ($n = 836$) concluded that the progression of nondiabetic renal disease was more rapid in men than in women, while three others ($n = 751$) found no significant gender difference in renal disease progression.

Using a fixed-effects model, the overall effect size (d) for the association between male gender and renal disease progression was 0.3619 (95% CI, 0.27 to 0.45) (Figure 1). The positive association was highly significant (mean weighted correlation [r] = 0.1781, $P < 0.00001$). All correlation coefficients were positive in the direction of an unfavorable renal outcome in males. The Q statistic was not significant, indicating homogeneity of effect size ($Q = 12.238$, $P = 0.1409$).

Meta-analysis using the fixed-effects model was repeated using four studies (7,10,12,13) that contained 1664 patients, after exclusion of four studies that used an outcome measure other than ESRD requiring renal replacement therapy or a decline in isotopically determined GFR. Excluded studies used a rise in serum creatinine ($n = 3$) or a decline in creatinine clearance ($n = 1$) as an outcome measure. The overall effect size for the association between male gender and renal disease progression was 0.3036 (95% CI, 0.20 to 0.41). The positive association was highly significant (mean weighted correlation [r] = 0.1501, $P < 0.00001$). All correlation coefficients were positive in the direction of an unfavorable renal outcome in males. The Q statistic was not significant, indicating homogeneity of effect size ($Q = 2.418$, $P = 0.6593$).

Calculations were repeated using a random-effects model (5). The overall effect size for the association between male gender and renal disease progression was 0.25601, indicating that male gender was associated with a worse outcome in chronic renal disease. The Q statistic was not significant, indicating homogeneity of effect size ($Q = 1.21852$, $P > 0.05$). Meta-analysis using the random-effects model was repeated using the four studies (7,10,12,13) that utilized ESRD or change in isotopically determined GFR as an outcome measure. The overall effect size for the association between male gender and renal disease progression was 0.25601. The Q statistic was not significant, indicating homogeneity of effect size ($Q = 0.365992$, $P > 0.05$).

IgA Nephropathy

Twenty-five studies (13,20–42,48), containing a total of 3127 patients, were selected for meta-analysis (Table 1). The mean age of the patients was 26.0 ± 2.1 yr with an mean follow-up of 63.6 ± 9.7 mo. Five studies were performed in a pediatric population, while the remaining studies included only adults. Thirteen other studies (44–47,49–56) ($n = 1967$) could not be included in the analysis because they did not report sufficient statistical data to calculate effect size. Twelve of 13 excluded studies found no significant gender difference in renal disease progression. Using a fixed-effects model, the overall effect size for the association between male gender and renal disease progression was 0.2012 (95% CI, 0.12 to 0.28) (Figure 2). The positive association was highly significant (mean weighted correlation [r] = 0.1001, $P < 0.00001$). Twenty-one of the 25 correlation coefficients were positive in the direction of an unfavorable renal outcome in males. The Q statistic was significant, indicating heterogeneity of effect size ($Q = 64.468$, $P < 0.00001$).

Meta-analysis was repeated using 16 studies (13,21,22,24,26,27,32–40,42) that contained 1464 patients, after exclusion of nine studies that used an outcome measure other than ESRD or a decline in isotopically determined GFR. Excluded studies used a rise in serum creatinine ($n = 5$), a decline in creatinine clearance ($n = 1$), or the development of "chronic renal failure" ($n = 3$) as an outcome measure. The overall effect size for the association between male gender and renal disease progression was 0.1428 (95% CI, 0.03 to 0.25). The positive association was significant (mean weighted correlation [r] = 0.0712, $P = 0.0043$). Thirteen of the 16 correlation coefficients were positive in the direction of an unfavorable renal outcome in males. The Q statistic was significant, indicating heterogeneity of effect size ($Q = 51.042$, $P < 0.00001$).

Calculations were repeated using a random-effects model (5). The overall effect size for the association between male gender and renal disease progression was 0.234743, indicating that male gender was associated with a worse outcome in IgA nephropathy. The Q statistic was not significant, indicating homogeneity of effect size ($Q = 2.443954$, $P > 0.05$). Meta-analysis using the random-effects model was repeated using the 16 studies (13,21,22,24,26,27,32–40,42) that used ESRD or change in isotopically determined GFR as an outcome measure. The overall effect size for the association between male gender and renal disease progression was 0.201413. The Q statistic was not significant, indicating homogeneity of effect size ($Q = 2.076299$, $P > 0.05$).

Membranous Nephropathy

Twenty-one studies (13,43,57–75), containing a total of 1894 patients, were selected for meta-analysis (Table 1). The mean age of the patients was 43.9 ± 1.3 yr with an average follow-up of 83.7 ± 11.9 mo. Five other studies (76–80) ($n = 651$) could not be included in the analysis because they did not report sufficient statistical data to calculate effect size. All five excluded studies found no significant gender difference in renal disease progression. Using a fixed-effects model, the overall effect size for the association between male gender and renal disease progression was 0.2309 (95% CI, 0.14 to 0.32) (Figure 3). The positive association was highly significant (mean weighted correlation [r] = 0.1147, $P < 0.00001$). In 17 of 23 studies, correlation coefficients were positive in the direction of an unfavorable renal outcome in male patients. The Q statistic was significant, indicating heterogeneity of effect size ($Q =$

Table 1. Studies analyzed by meta-analysis[a]

	Year of Publication	Mean Age (yr)	*n*	Men	Women
Chronic renal disease					
Coggins (7)	1998	52	585	357	228
Coggins (7)	1998	52	255	151	104
Hannedouche (8)	1993	51	223	126	97
Hunt (10)	1998	37	246	156	90
Jungers (9)	1995	46	159	108	51
Rosman (11)	1989		113	62	51
Ruggenenti (12)	1998	52	98	79	19
Simon (13)	1994		480	99	381
Williams (14)	1998		70	47	23
IgA nephropathy					
Alamartine (20)	1991	28	282	222	60
Berg (38)	1993	9	36	22	14
Bogenshutz (21)	1990	33	239	176	63
Boyce (33)	1986	35	112	90	22
Chida (22)	1985	28	81	43	38
D'Amico (48)	1985	30	92	57	35
Droz (23)	1984		244	173	71
Frimat (24)	1997	36	210	173	37
Hogg (42)	1994	11	80	57	23
Hood (27)	1981	26	37	27	10
Kobayashi (36)	1988	30	29	15	14
Kobayashi (37)	1989	34	42	21	21
Levy (40)	1985	9	91	63	28
Nicholls (28)	1983	32	212	155	57
Packham (25)	1996		204	106	98
Propper (29)	1987	29	61	51	10
Rambausek (35)	1987	33	131	90	41
Rekola (26)	1991	38	77	60	17
Simon (13)	1994		161	72	89
Van der Peet (32)	1977	28	25	21	4
Velo (30)	1987	22	97	61	36
Woo (34)	1987	26	151	110	41
Wyatt (31)	1993	36	128	90	38
Wyatt (39)	1995	11	103	70	33
Yoshikawa (41)	1992	10	200	122	78
ADPKD					
Bear (81)	1992		42		
Choukroun (82)	1995	46	109	57	52
Choukroun (82)	1995	49	48	27	21
Conte (91)	1995		325	136	189
Conte (91)	1995		642	321	321
Geberth (88)	1995		74	40	34
Geberth (88)	1995		74	44	30
Gonzalo (89)	1996		82	52	30
Gonzalo (90)	1996	32	30	6	24
Higashihara (86)	1992		72	42	30
Johnson (83)	1997		388		
MDRD (84)	1995		141	79	62
MDRD (84)	1995		59	34	25
Simon (92)	1995		63	30	33
Stewart (85)	1994		1157	630	527
Torra (87)	1996		38		

Table 1.—Continued

	Year of Publication	Mean Age (yr)	*n*	Men	Women
Membranous nephropathy					
Abe (57)	1986	39	89	45	44
Bone (74)	1996	50	42	25	17
Cameron (58)	1990	45	103	87	16
Collaborative (59)	1979		72	42	30
Davison (60)	1984		62	45	17
Donadio (73)	1988	50	140	93	47
Durin (72)	1990		82	48	34
Fuiano (61)	1989	49	25	14	11
Honkanen (62)	1994	41	72	53	19
Hopper (63)	1981	43	100	65	35
Hunt (75)	1992	40	83	60	23
Jindal (64)	1992	50	26	22	4
MacTier (65)	1986	43	26	22	4
Murphy (43)	1988	36	139	77	62
Ponticelli (66)	1984	44	62	49	13
Ramzy (67)	1981	35	35	18	17
Schieppati (68)	1993	51	100	68	32
Simon (13)	1994		85	43	42
Toth (69)	1994	43	100	52	48
Tu (70)	1984	44	117	75	42
Wehrmann (71)	1989		334	223	111

[a] ADPKD, autosomal dominant polycystic kidney disease.

35.624, $P = 0.0333$). Meta-analysis was repeated using a fixed-effects model with 12 studies (13,43,63–65,67,68,70–73,75) that contained 1267 patients, after exclusion of nine studies that used an outcome measure other than ESRD or a decline in isotopically determined GFR. Excluded studies used a rise in serum creatinine ($n = 5$) or the development of "chronic renal failure" ($n = 4$) as an outcome measure. The overall effect size for the association between male gender and renal disease progression was 0.3188 (95% CI, 0.20 to 0.44). The positive association was highly significant (mean weighted correlation [r] = 0.1574, $P < 0.00001$). In 10 of the 12 studies, correlation coefficients were positive in the direction of an unfavorable renal outcome in males. The Q statistic was not significant, indicating homogeneity of effect size ($Q = 12.908$, $P = 0.2994$).

Calculations were repeated using a random-effects model (5). The overall effect size for the association between male gender and renal disease progression was 0.21635, indicating that male gender was associated with a worse outcome in membranous nephropathy. The Q statistic was not significant, indicating homogeneity of effect size ($Q = 3.015111$, $P > 0.05$). Meta-analysis using the random-effects model was repeated using the 12 studies (13,43,63–65,67,68,70–73,75) that utilized ESRD or change in isotopically determined GFR as an outcome measure. The overall effect size for the association between male gender and renal disease progression was 0.330358. The Q statistic was not significant, indicating homogeneity of effect size ($Q = 1.44415$, $P > 0.05$).

ADPKD

Twelve studies (81–92), containing a total of 3344 patients, were selected for meta-analysis (Table 1). Four other studies (93–96) ($n = 349$) were not included in the analysis because they did not report sufficient statistical data to calculate effect size. All four excluded studies found no significant gender difference in renal disease progression. Using a fixed-effects model, the overall effect size for the association between male gender and renal disease progression was −0.1516 (95% CI, −0.22 to −0.08) (Figure 4). The negative association achieved statistical significance (mean weighted correlation [r] = −0.0756, $P < 0.00001$). The Q statistic was significant, indicating heterogeneity of effect size ($Q = 830.932$, $P < 0.00001$). Despite the fact that 10 of the 12 studies showed a positive correlation coefficient in the direction of an unfavorable renal outcome in males, one egregious outlier (91) ($n = 967$) led to an overall negative effect size. Removal of this outlier resulted in a significant positive overall effect size ($d = 0.2818$, 95% CI, 0.20 to 0.36, $r = 0.1395$, $P < 0.00001$, $Q = 27.955$, $P = 0.0092$), indicating that male gender was associated with more rapid progression of ADPKD.

Meta-analysis was repeated with a fixed-effects model using eight studies (81,83–89) that contained 2127 patients, after exclusion of four studies that used an outcome measure other than age of onset of renal replacement therapy or a decline in isotopically determined GFR. Excluded studies used a rise in serum creatinine ($n = 3$) or a decline in creatinine clearance ($n = 1$) as an outcome measure. The overall effect size for the

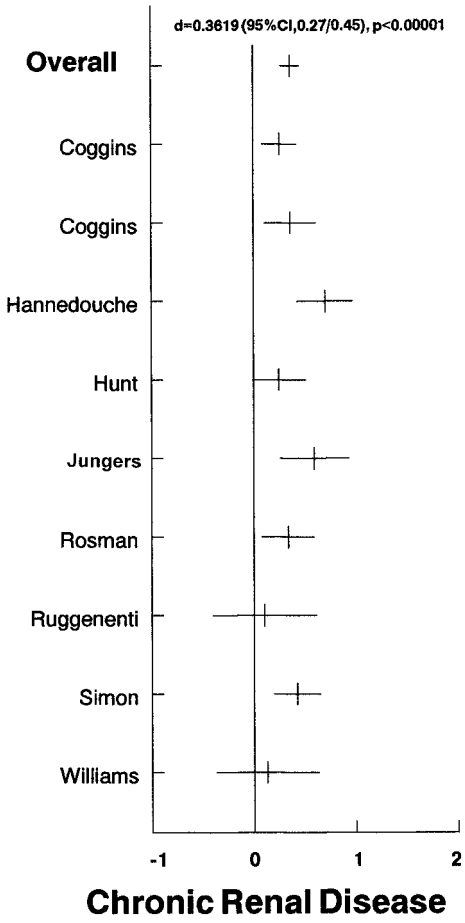

Figure 1. Effect size and 95% confidence interval (CI) for individual studies of the effect of gender on the progression of chronic renal disease of mixed etiology. The overall mean effect size and 95% CI is shown on top. A positive value indicates that male gender is associated with an adverse renal outcome.

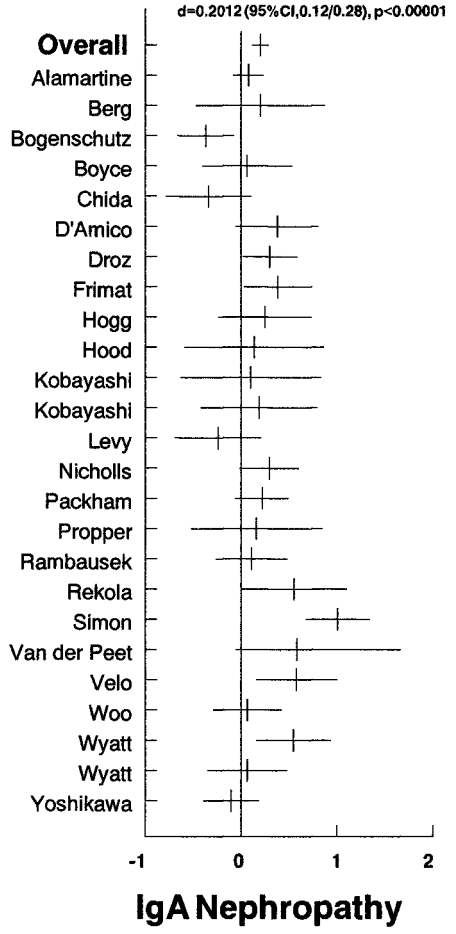

Figure 2. Effect size and 95% CI for individual studies of the effect of gender on the progression of IgA nephropathy. The overall mean effect size and 95% CI is shown on top. A positive value indicates that male gender is associated with an adverse renal outcome.

association between male gender and renal disease progression was 0.2469 (95% CI, 0.16 to 0.33). The positive association was significant (mean weighted correlation [r] = 0.1225, $P <$ 0.00001). In seven of the eight studies, correlation coefficients were positive in the direction of an unfavorable renal outcome in males. The Q statistic was not significant, indicating homogeneity of effect size (Q = 13.422, P = 0.1444).

Results obtained using a random-effects model (5) differed from those obtained with the fixed-effects model. The overall effect size for the association between male gender and renal disease progression was 0.07955, indicating that male gender was associated with a worse outcome in ADPKD. The Q statistic was not significant, indicating homogeneity of effect size (Q = 14.6004, $P > 0.05$). Meta-analysis using the random-effects model was repeated using the eight studies (81,83–89) that utilized age of onset of renal replacement therapy or a decline in isotopically determined GFR as an outcome measure. The overall effect size for the association between male gender and renal disease progression was 0.351261. The Q statistic was not significant, indicating homogeneity of effect size (Q = 1.363283, $P > 0.05$).

Meta-Regression Analysis

We performed a meta-regression analysis to delineate possible reasons for heterogeneity among the studies. The analysis revealed no significant relationship between standardized effect size and the following variables: year of publication, total number of subjects, number of male subjects, number of female subjects, mean patient age, year of study publication, immunosuppressive therapy, minimum duration of follow-up, mean duration of follow-up, outcome measure, study quality, or type of renal disease.

A funnel plot was constructed of standardized effect size *versus* subject number (Figure 5). The equal distribution of points above and below the mean standardized effect size for small n values suggests the absence of "file-drawer publication bias" (6).

Discussion

Although we have hypothesized that gender influences the progression of nondiabetic chronic renal disease, this is not a view shared by all investigators (1,2). Individual published reports have yielded conflicting results (1). This is not surprising since variability may arise due to small numbers of subjects

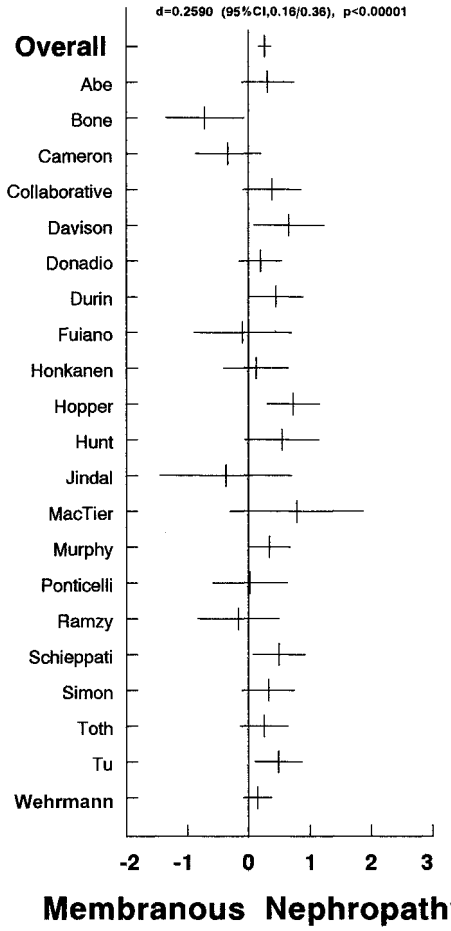

Figure 3. Effect size and 95% CI for individual studies of the effect of gender on the progression of membranous nephropathy. The overall mean effect size and 95% CI is shown on top. A positive value indicates that male gender is associated with an adverse renal outcome.

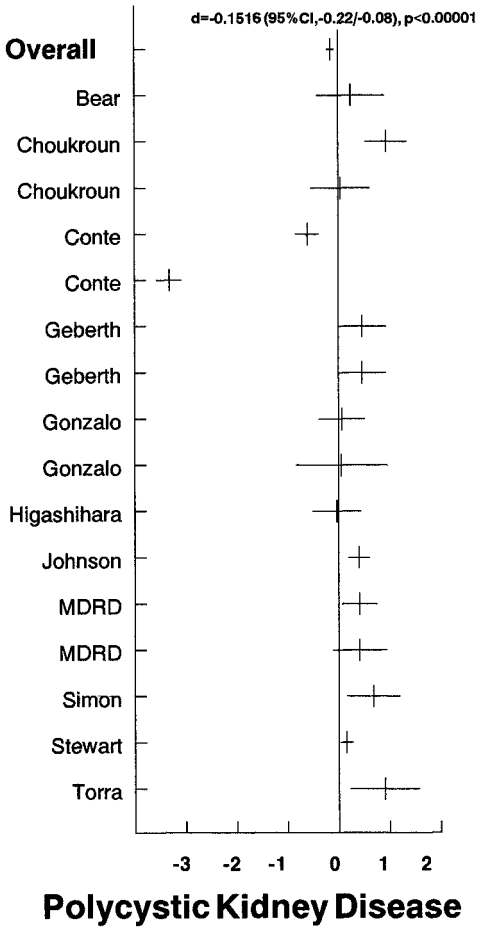

Figure 4. Effect size and 95% CI for individual studies of the effect of gender on the progression of autosomal dominant polycystic kidney disease. The overall mean effect size and 95% CI is shown on top. A negative value indicates that female gender is associated with an adverse renal outcome.

or short patient follow-up. Also, different treatment regimens may obscure any effects of gender on renal disease outcome. The debate is intensified by the paucity of prospective studies with large sample size and extended patient follow-up. Under these circumstances, any nonanalytical overview of the published literature is subject to bias. In light of these issues, we conducted a meta-analysis to determine the effect of gender on the progression of nondiabetic chronic renal disease.

Our meta-analysis clearly indicates that gender is an important factor influencing the progression of nondiabetic chronic renal disease. However, meta-analysis is itself subject to numerous inherent limitations. The first of these is publication bias. Few studies have been performed specifically to evaluate the role of gender on renal disease progression. Studies in which the investigators did not find gender to be a significant covariate may not report gender-specific statistical data. These negative unreported or under-reported results are obviously lost to the meta-analysis. However, a funnel plot of our data failed to reveal any such "file drawer bias."

In addition, we carefully analyzed all studies that were excluded from our meta-analysis because they failed to report sufficient statistical data. Most of the excluded studies concluded that gender had no significant effect on renal disease progression. Although this result appears to detract from the validity of the meta-analysis, it is important to note that a study may fail to find a significant difference between men and women but still yield a positive effect size in favor of an adverse renal outcome in men and thus contribute to an overall positive effect size. In fact, this occurred with many of the studies included in our meta-analysis.

Studies that assess the rate of decline in renal functions by measuring serum creatinine levels or time until dialysis in men *versus* women must be interpreted cautiously. Men ingest more protein and have a larger muscle mass than women, which accounts for an increased rate of creatinine generation. This may contribute to apparent gender-related differences in renal disease progression in studies relying only on serum creatinine measurements to assess renal function. To address this issue, we repeated our meta-analyses after excluding all studies that used serum creatinine as an end point. When we restricted our analysis to studies that used ESRD requiring renal replacement therapy or a decline in true GFR as an outcome measure, male

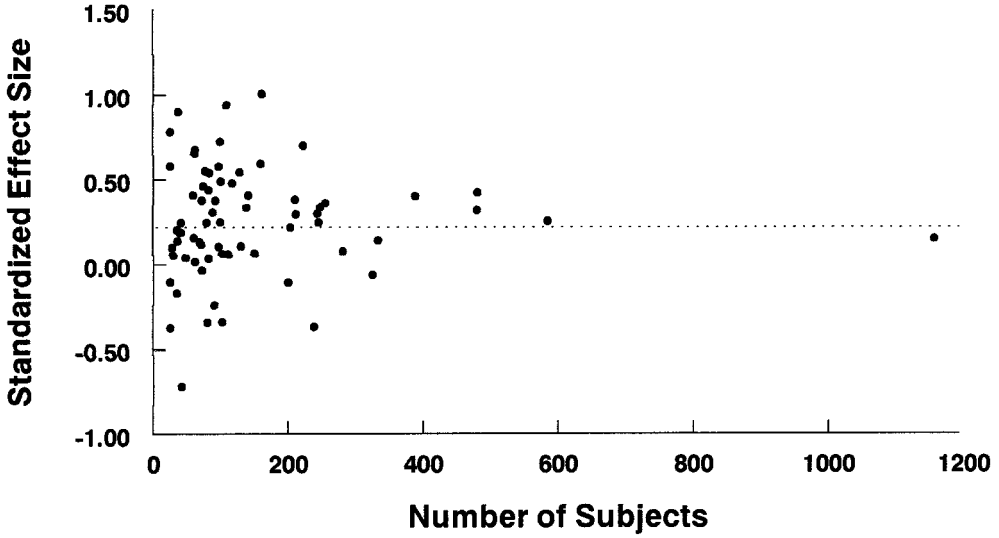

Figure 5. Funnel plot of standardized effect size *versus* subject number. The horizontal line shows the mean standardized effect size. One outlier study (91) falls off the plot ($n = 642$, $d = -3.32$).

gender again adversely influenced the outcome of chronic renal disease.

The quality of a meta-analysis is no better than that of its component studies. Many of the studies we analyzed were retrospective with limited sample size and limited duration of patient follow-up. Others used less than ideal outcome measures or failed to adequately report or analyze censored subjects. However, the overall validity of our conclusion is supported by the highly significant association obtained between male gender and adverse renal outcome in our analysis of CRD, IgA nephropathy, and membranous nephropathy. This was true using both the fixed-effects and random-effects models. In addition, the individual correlation coefficients in the large majority of studies were positive, suggesting that the overall positive effect size was not due to chance alone. Moreover, the effect sizes were homogeneous in the CRD analysis. In the membranous nephropathy and IgA nephropathy meta-analyses, homogeneity of effect size was present when a random-effects model was used and could be achieved with the fixed-effects model by merely eliminating one or two outlier studies (data not shown).

A detailed discussion of our ADPKD data is warranted. Despite the fact that 11 of the 13 studies showed a positive correlation coefficient in the direction of an unfavorable renal outcome in men, one egregious outlier (91) led to the opposite result using a fixed-effects model. Removal of the flagrant outlier resulted in a significant *positive* overall effect size, indicating that male gender was associated with more rapid progression. However, a random-effects model may be a more appropriate model to use, given the marked heterogeneity among the studies. In fact, the random-effects model of DerSimonian and Laird (5) yielded a positive overall effect size, indicating that male gender was associated with a worse outcome in ADPKD.

The outlier study was performed by the Italian ADPKD Cooperative Study Group and was reported in a non-peer-reviewed publication (91). This prospective study performed serial measurements of serum creatinine over 54 mo in 325 hypertensive and 642 normotensive subjects with ADPKD and a baseline serum creatinine value <1.4 mg/dl. These investigators found a more rapid rate of progression in women compared with men, especially among normotensive subjects. In contrast, the Modification of Diet in Renal Disease Study, a prospective multicenter study that included 141 subjects with ADPKD and moderate impairment of function, found a significantly greater decline in renal function, measured by iothalamate clearance, in men with ADPKD compared with women (84). In addition, five studies have used multivariate analysis to assess the effect of gender on the rate of progression of ADPKD (82–84,91,97). All but the outlier study concluded that male gender was an independent factor contributing to more rapid progression of ADPKD. The reason for these conflicting results is unclear. Although several studies suggest that sexual dimorphism in renal disease progression is seen only in the early stages of ADPKD and is lost in patients with advanced renal impairment (84,92,98), this observation cannot explain the divergent results since the outlier study did not include subjects with severe renal impairment. Perhaps the use of serum creatinine as an outcome measure contributed to the anomalous result in the outlier study.

Our meta-analysis clearly indicates that gender is an important factor influencing the progression of some nondiabetic chronic renal diseases. However, we were unable to determine whether the presence of testosterone or the absence of estrogen is a determining factor. Moreover, we were unable to assess whether any renoprotective effects of female gender are limited to premenopausal women, as would be expected if estrogen is critical. In this regard, two prospective studies suggest that the renal protection afforded by female gender is only evident in premenopausal women (7,13). Moreover, our analysis cannot assess whether the effects of gender on renal disease progression are independent of other covariates such as diet, BP, or

serum lipid levels. Our laboratory has performed *in vitro* studies that indicate that sex hormones have effects on mesangial cell biology that may directly influence the course of chronic renal disease (1,99–106). Other investigators have shown that manipulation of the hormonal environment influences the progression of experimental models of chronic renal disease (1). Although the effects of sex hormones on dietary intake, BP, and serum lipid levels were not measured in most of these studies, sex hormones can influence the progression of experimental renal disease independent of these factors (1).

An independent role for gender in the progression of renal disease in humans has not been clearly established (1). Few studies used multivariate analysis to evaluate the role of gender in renal disease progression. Moreover, the results of these multivariate analyses have been conflicting. Six studies used multivariate analysis to analyze the effect of gender on the rate of progression of chronic renal disease of mixed etiologies (7–10,16,107). Three of these studies showed male gender to be an independent determinant of adverse renal outcome, whereas three others did not. By univariate analysis, the Modification of Diet in Renal Disease Study identified male gender as a risk factor for more rapid decline in renal function in 840 primarily nondiabetic subjects with chronic renal disease (7). However, multivariate analysis showed that only proteinuria, HDL levels, and BP independently contributed to a worse renal outcome (7).

Eleven studies used multivariate analysis to analyze the effect of gender on the rate of progression of IgA nephropathy (20,24,42,45,48–53,56). Only two of these studies found male gender to be an independent determinant of an adverse renal outcome, while nine others did not. Eleven studies used multivariate analysis to analyze the effect of gender on the rate of progression of membranous nephropathy (62,69–71,73,75–79). Four of these studies found male gender to be an independent determinant of an adverse renal outcome, while seven others did not. Consistent with our finding that male gender is associated with a less favorable course in patients with membranous nephropathy, two groups of investigators performed pooled patient analyses that yielded an identical conclusion (108,109). Hogan *et al.* (108) reviewed 32 studies that evaluated the outcome of membranous nephropathy and found that male gender was a significant predictor of reaching a renal end point. Reichert *et al.* (109) performed a pooled patient analysis of 810 male and 438 female subjects with membranous nephropathy included in 12 published studies and found that the odds ratio for deterioration of renal function in males was 3.5 (95% CI, 2.5 to 4.9). Similarly, Laluck and Cattran (110) found that lower levels of proteinuria and female gender were the only independent factors associated with remission of proteinuria in patients with membranous nephropathy.

In conclusion, our analysis of the published literature indicates that male gender is associated with a more rapid rate of progression and a worse renal outcome in patients with chronic renal disease.

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