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By

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ABSTRACT

SEX DIFFERENCES IN STROKE RECOVERY: RESULTS FROM THE MASCOTS OUTCOMES STUDY

By

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Background: Little is known about sex differences in stroke recovery. The few available studies have found that women are less likely to achieve independence in activities of daily living (ADL) and have poorer quality of life (QOL). **Methods**: A total of 373 stroke survivors from a hospital-based stroke registry were enrolled in the MASCOTS Outcomes Study. Follow-up data, including the Barthel Index (BI) and Stroke-Specific Quality of Life (SS-QOL), were obtained by telephone interview 90 days post-stroke. The independent effects of sex on ADL independence (BI≥95), controlling for age, race, stroke subtype, and other patient characteristics, were determined by logistic regression, and on SS-QOL scores by linear regression. Two-way interactions were considered. Least-squares means for SS-QOL scores were calculated to summarize the independent effects of sex. **Results**: Follow-up information was obtained on 72% (N=273) of subjects. In adjusted models, males were more likely to achieve ADL independence (OR 2.75, 95% CI 1.49-5.08). Females had lower adjusted SS-QOL scores in Physical Function, Thinking, Language, and Energy. Interactions between sex and diabetes history, prior stroke, or interview source were found for Mood, Role Function, Vision and Summary Scores. **Conclusions**: Females are at a disadvantage in stroke recovery. These differences are not explained by females' greater age at stroke onset or other measured patient characteristics.

Dedicated to Joel, who always knew I could do it

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INTRODUCTION

The Institute of Medicine has recommended that "sex should be considered when designing, analyzing, and reporting findings from studies in all areas and at all levels of biomedical research [1]" Many studies have investigated sex differences in symptoms, management, and outcomes of cardiovascular disease (for reviews, see [2-4]). Less is known about sex differences in stroke. Stroke is a leading cause of death in the United States, ranking third for females and fourth for males [5]. Although the age-adjusted rates of stroke mortality are similar for men and women, women have higher stroke death rates overall (68.2 vs. 44.2 per 100,000 in 2002) owing to women's higher average age at stroke presentation [5]. One large population-based study found sex differences in case fatality in older age groups [6], and a large European study found men were more likely to survive to 28 and 90 days [7]. However, other studies found no significant differences in stroke survival by sex [8, 9].

Because of stroke's potential for profound and prolonged negative consequences on health and well-being, it is important to document the health states of stroke survivors discharged from the hospital. The World Health Organization has adopted the International Classification of Functioning, Disability and Health (ICF) as a new framework for describing health states [10]. The ICF replaces the International Classification of Impairments, Disabilities, and Handicaps (ICDIH), a system that had been criticized as inconsistent and confusing [11]. The ICF model describes interrelationships between health conditions, environmental factors, and personal factors with three interrelated

areas of functioning: body structures, activity performance, and participation. In the ICF, negative health states involving body structures at the organ level are referred to as impairments, difficulties with task performance are called activity limitations, and poor outcomes relating to involvement in life situations, reflecting personal and environmental factors, are called participation restrictions [10].

An adaptation of the ICF framework to illustrate the relationship of sex to stroke outcomes is illustrated in Figure 1. Sex is located among the personal and environmental contextual factors, where it may modify their effects. "Sex" refers to an organism's biological classification based on chromosomes and reproductive organs, while "gender" refers to "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 [1]." While many factors in Figure 1, such as social roles, response of health care systems to patients, and expectations, are closely tied to a person's gender presentation and identity, because this presentation is so heavily influenced by biological sex, we will refer to "sex differences" throughout this paper. Sex is related to other variables inherent to the individual, including age at stroke onset, psychological state, educational background, values, and expectations. These personal attributes influence and are influenced by other contextual factors on the individual and societal levels. In these ways, sex may influence the quality of healthcare a patient is receives in the emergency department, and could affect a stroke patient's recovery. For example, reintegration with the community may be affected by sex influences on social roles or the workplace. Together, these

personal and environmental factors could directly and indirectly affect functional outcomes on multiple levels -- including body organs, activities, and participation. In turn, because a person's lifestyle and health behaviors are shaped by their impairments, activity limitations, and participation restrictions, sex may influence stroke risk and recurrence. Underlying biological differences in brain structure and function between the sexes could lead to differences in symptom profiles between men and women, and could influence the capacity for recovery or adaptation to brain injury. These direct biological effects are noted by the dashed line in the figure. Finally, personal factors -- including sex -- interact with a person's functional capacity to shape an individual's quality of life (QOL). In Figure 1, QOL is represented as a separate outcome, since according to Stucki, "quality of life refers to global or highly personalized evaluations of functioning *referring to satisfaction or feelings*" (emphasis added), and falls outside the ICF framework [10]. In this model, two patients with identical brain lesions, leading to similar impairments, activity limitations, and participation restrictions, could experience vast differences in QOL, depending on how they feel about their level of functioning. These individualized responses to life circumstances may differ considerably for men and women. Therefore, sex can influence QOL directly outside of its influence on functional status.

Stroke burden is experienced by both men and women, but because of differences in factors such as anatomy and physiology, age at stroke onset, expectations, psychological state, social support, family networks, and interactions with the healthcare system, the sexes may experience important

differences in outcomes. Awareness of sex differences in morbidity and QOL following a stroke may enable better targeting of prevention, intervention, and rehabilitation services to relevant populations. Several studies have found that women who survive stroke have less favorable outcomes. Women are less likely to be discharged home than men [6, 8, 9] and are more likely to have impairments and activity limitations on follow-up [7, 9, 12, 13]. Women may experience more mental impairment [8], depression [14], and fatigue [15], and lower overall quality of life (QOL) [16] than men following stroke. In cohort-based studies, various investigators have found sex differences in stroke presentation [8, 9, 17, 18] and medical history. Although stroke occurs at a later age in women, adjustment for age and other sex differences in medical history and presentation have not eliminated the differences in outcomes noted above.

The Paul Coverdell National Acute Stroke Registry (PCNASR) is being developed to monitor the quality of stroke care in the United States. Of states participating in the initial pilot phase of the PCNASR, only the Michigan prototype, called the Michigan Acute Stroke Care, Outcomes and Treatment Surveillance System (MASCOTS), conducted a follow-up study of stroke admissions after hospital discharge. The MASCOTS Outcomes Study (MOS) therefore provides a unique opportunity to study the relationship between patient demographic and clinical characteristics, as well as features of hospital care, and stroke outcomes following hospital discharge in a sample from the United States.

The objectives of this study are to determine the magnitude of sex differences in stroke outcomes at three months, including survival, disability, and

quality of life, in subjects discharged from a hospital-based state-wide stroke registry. Based on the findings of others, we expected that women would be less likely to achieve a independence in ADL. We hypothesized that, after controlling for potential confounders measured at baseline such as demographics, stroke characteristics and comorbidities, women would report lower scores in the Physical Function, Mood, and Energy domains of the SS-QOL. Because little is known about the influence of sex on the other domains of the SS-QOL, our analyses of these domains is exploratory, rather than hypothesis-driven. Finally, we hypothesized that adverse health events in the post-discharge period would negatively impact ADL independence and QOL at 3 months.

METHODS

Registry Design and Case Ascertainment

MASCOTS, a statewide hospital-based acute stroke registry, was a prototype for the Paul Coverdell National Acute Stroke Registry. A modified stratified sampling scheme based on a single-stage cluster design was used to obtain a representative state-wide sample of 16 hospitals. An inception cohort design was followed, wherein all subjects admitted to the 16 participating hospitals between May 2002 and November 2002 were identified prospectively and enrolled in the registry. The registry included a broad range of stroke subtypes, including ischemic stroke (IS), intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH) and transient ischemic attack (TIA). Detailed chart-level information was collected on 2566 admissions in the MASCOTS registry. This included information on demographics, stroke subtype, past medical history, pre-stroke and post-stroke ambulatory status, and Modified Rankin Score (mRS) at discharge.

Outcomes Study

Nine of the 15 hospitals who completed the 6 month data collection agreed to participate in the MASCOTS Outcomes Study (MOS) (Figure 2). Hospitals were instructed to approach all consecutive admissions who met the inclusion criteria beginning in September 2002, with the goal of consenting 50 subjects prior to their discharge. All hospitalized acute stroke cases were eligible for the study, except those that obviously had very poor prognosis (defined in the study protocol as a life expectancy of less than 6 months as noted in the

subject's medical record) or were discharged to hospice care. Subjects who had strokes while in the hospital for other reasons and subjects who died in hospital were ineligible for the study. When possible, informed consent was obtained from the patient. However, for patients who were unable to complete the consent process on their own due to language difficulties or cognitive impairments, a next of kin or legal guardian present in the hospital at the time of consent was sought as a proxy consent. Patients or proxies who could not complete a follow-up telephone interview in English were excluded. The same detailed chart abstraction used in the registry was collected on all subjects in the outcomes study.

Follow-up Interviews

Trained interviewers from the Survey Research Center, University of Michigan School of Public Health, conducted two waves of telephone surveys: approximately 90 days and one year after the subjects were discharged. The interview included the Barthel Index (BI) and Stroke-Specific Quality of Life (SS-QOL). In addition, information was gathered on the use of health care services post-discharge, including home health and rehabilitation services, physician's office visits, emergency department visits, and planned and emergency overnight hospitalizations. A separate questionnaire, containing the same questions but with slight wording changes, was developed for the proxy interviews.

Death Certificate Search

A death certificate search was conducted by the Division of State Records, Michigan Department of Community Health, on all enrolled subjects who did not complete the wave 1 interview (either because they refused, were lost to follow-up or had died). Information on the date of death, underlying cause of death (UCOD), and contributing causes were abstracted.

Definition of Exposure Variables

Three categories of stroke sub-type were created based on those defined by the Coverdell stroke registries: ischemic stroke (IS, ischemic stroke and ischemic stroke of uncertain duration), hemorrhagic stroke (HS, intracerebral hemorrhage, subarachnoid hemorrhage, and hemorrhagic stroke of uncertain type), and transient ischemic attack (TIA). Because only a small number of subjects were completely unable to walk, ambulatory status pre-stroke and at discharge were dichotomized as independent vs. dependent (i.e., requiring assistance or unable to ambulate). Past medical history information, including diagnoses of hypertension, diabetes mellitus, prior stroke/TIA, and heart disease (defined as myocardial infarction and/or coronary heart disease) was dichotomized as definitely present vs. absent/no information recorded. Smoking status was dichotomized as current smoker vs. other (includes former and never smokers). Race/ethnicity was categorized as white vs. nonwhite, with nonwhite including African American, Hispanic, Native American, Asian/Pacific Islander, and other. The vast majority of non-whites were African American. Age was maintained as a continuous variable in all analyses unless otherwise noted.

Physician visits prior to the wave 1 interview were collected in four categories: none, one, 2-5, and 6 or more. Other health care services, including emergency hospitalizations, rehabilitation services, and home health services, were dichotomized into ever vs. never used.

Stroke Outcome Measures

Because stroke can influence many aspects of health, and can result in impairment, activity limitations, participation restrictions, and lower quality of life, stroke outcome measures have been developed to assess these dimensions. Outcome measures employed in this study are summarized in Table 1.

The modified Rankin Scale (mRS), a single item scale with six levels, is often termed a measure of handicap, but its language actually refers to both activity limitations ("able to walk without assistance") and participation restrictions ("able to look after own affairs"). We will use the generic term "disability" for mRS, since that word is employed in the definitions of the scale's levels. Floor and ceiling effects are non-existent based on the definitions of the scale (ranging from "no symptoms" to "requiring constant nursing care and attention"). In terms of content validity, the scale covers primarily mobility and continence, but does not consider communication and cognition [19]. Construct validity has been established through correlations with BI and the NIH Stroke Scale [19]. Inter-rater reliability has ranged from .3 to .8 in various studies [19]. Particular concern has been expressed over unreliable scoring of the middle categories [20]. For this analysis, mRS which is recorded as a single item six point scale, was

dichotomized into no or slight disability (0-2) vs. moderate to severe disability (3-5), a cutpoint that has been used in several clinical trials [21].

The Barthel Index (BI) is a widely accepted measure of functional capacity in activities of daily living (ADL). It has been found to be valid and reliable [22]. The index is scaled from 0 (completely dependent in ADL) to 100 (no ADL limitations) in 5-point increments and measures independence in the following areas: feeding, bathing, grooming, dressing, bowel and bladder continence, toilet use, bed to chair transfers, mobility on level surfaces, and stair climbing [23]. Because many stroke patients experience subtle impairments that do not affect their ability to perform ADL, the BI has a recognized ceiling effect in the stroke population. Patients who achieve perfect scores on this instrument may continue to improve, but the BI will not be able to evaluate these changes. Such patients may still have important functional detriments that preclude independent living, but they generally do not need an attendant [23]. A score of 95 on the BI is commonly used as measure of independence in ADL [12, 21]; we used this as our outcome measure.

Although recovery in basic ADL is an important achievement that may allow stroke survivors to live independently, many patients experience residual deficits that negatively impact their lives in spite of ADL independence. Quality of life instruments aim to measure subjective well-being in various dimensions, including physical, emotional and social aspects. Many generic quality of life instruments, such as the SF-36, have been used in stroke survivors. Generic measures may not have strong content validity when applied to stroke, however,

because stroke survivors commonly experience effects that are not assessed by generic instruments [24, 25]. Because existing generic measures did not adequately measure many consequences of stroke, such as hand function, communicative abilities, and cognition, two measures of quality of life specific to stroke were developed in the late 1990s: the Stroke Impact Scale (SIS) [26] and Stroke-Specific Quality of Life (SS_QOL) [27].

The SS-QOL was designed to assess QOL in stroke survivors across the breadth of stroke's potential effects on health. The SS-QOL was initially developed in a cohort of mild to moderate ischemic stroke survivors with the goal of creating an outcome measure that would assess aspects of health that were relevant and important to stroke survivors, and that would be able to evaluate change in health status over time [27]. In developing the SS-QOL, a large pool of questions was generated through interviews with stroke survivors to maximize content validity. The number of items was reduced after administering a questionnaire to stroke survivors 1 and 3 months after their events on the basis of exploratory factor analysis and internal consistency [27]. The instrument was originally published as a 49-item, 12 domain scale (version 2), and was later reduced to the 35-item, 7 domain scale (version 3) used in this study with some reassignment of items to new domains and other minor modifications [28]. The SS-QOL maintains strong content validity for measuring stroke outcomes [27]. The SS-QOL may be validly and reliably administered by telephone [29].

The SS-QOL v.3 consists of 35 questions each of which receive a score of 1 to 5, with higher numbers indicating better health [28]. These questions are

assigned to seven individual domains, with a range of three to ten items per domain. Scores for each SS-QOL domain are calculated by averaging the non-missing item scores in that domain; if half or more of the item responses are missing, the domain score is defined as missing for that patient. Therefore, each domain score is a continuous variable with a minimum value of 1 (worst) and a maximum value of 5 (best). The SS-QOL Summary Score, an overall measure of QOL in stroke survivors, is calculated by averaging the seven domain scores [28].

The individual SS-QOL domains measure the patient's assessment of the difficulty they experience in each of the seven domains [25, 27, 28]. Physical Function questions relate to difficulty with mobility, work, self care, and arm or hand function. The Language questions relate to difficulty speaking and being understood. Vision questions assess ability to see well enough to do particular things such as watch television or reach for objects. The Thinking domain assesses whether the subject notices difficulty with memory or concentration. The Energy questions ascertain feelings of fatigue and their effects on activities. The Mood domain focuses on depression-related feelings. Role Function questions ascertain whether the subject participates in activities with friends and family to the degree desired.

Descriptive Statistics and Bivariate Analyses

The analyses in this report are confined to the first wave of interviews conducted beginning 3 months post-discharge. For each patient, the detailed chart information was linked to the follow-up interview data and death certificate information where applicable.

To assess the possibility of selection bias into the outcomes study cohort, bivariate analyses were conducted to compare several demographic and clinical variables between MOS subjects and MASCOTS registry subjects. To assess non-response bias, similar analyses were performed to compare responders with non-responders.

Demographic and clinical characteristics of patients measured at baseline have the potential to confound the relationship between sex and stroke outcomes if they are related to both sex and the outcomes. To assess this possibility, males and females were compared with respect to baseline characteristics and medical system use prior to the wave 1 interviews. In addition, bivariate associations between the potential confounders and stroke outcomes were considered. Linear regression was used to examine the association between SS-QOL scores and age. Student's t-test and ANOVA were performed to examine associations between SS-QOL scores according to the following patient factors: sex, race, mRS grade, ambulatory status prestroke and at discharge, stroke subtype, and interview source (i.e., patient or proxy). Bivariate logistic regression was used to examine the association between the odds of achieving ADL independence (BI ≥ 95) and the following independent patient factors: age, gender, race, ambulatory

status pre-stroke and at discharge, stroke subtype, mRS, and interview source. Wald chi-square tests were performed to test the statistical significance of these bivariate associations. Statistical significance was defined by the conventional alpha level of 0.05.

Multivariable Modeling Strategies

The independent effect of sex on ADL recovery was assessed through a multiple logistic regression model. The model included age, race and stroke subtype as *a priori* confounders. Past medical history, ambulatory status pre-stroke and at discharge and interview source were also considered for inclusion. A parsimonious main effects model was developed by first creating a full model with all candidate predictors, then removing items through backwards elimination. The likelihood ratio chi-square test was used to assess the statistical significance of variables removed from the model. Variables were removed until all main effects other than the *a priori* confounders had p-values <.05. Biologically plausible two-way interaction terms were then entered into the model if at least five observations were present in all cells, and were eliminated sequentially until only statistically significant interaction terms remained. The Hosmer-Lemeshow goodness-of-fit test was used as a measure of model fit.

The effect of sex on SS-QOL domain and Summary Scores, controlling for other baseline patient characteristics, was tested through multiple linear regression. Modeling procedures were similar to those described for logistic regression. An F-test was performed to determine the statistical significance of variables removed during the backwards selection process. R^2 was used as a

measure of model fit. Least-squares means by sex were derived from the final multiple linear regression models to illustrate the magnitude of the independent effects of sex on SS-QOL scores. When a final model included a two-way interaction involving sex, least-squares means were calculated by sex within strata of the interacting variable. The influence of proxy responses was assessed by generating least-squares means from the baseline model excluding scores obtained from proxy respondents.

To determine whether adverse health events in the post-discharge period confounded the relationship between sex and stroke outcome, emergency hospitalizations were added to all regression models.

RESULTS

A total of 373 eligible subjects were consented and enrolled in the MOS (Figure 2), 72% (N=270) completed the follow-up interview. Three percent (N=15) had died, 13% (N=48) refused to participate when called, and 11% (N=42) were lost to follow-up. Proxy respondents were the source for 25% (N=68) of the interviews. The original enrollment goal of 450 subjects (50 per hospital) was not met primarily because of low enrollment at two sites (17 and 29 subjects, respectively). The seven remaining sites enrolled close to fifty subjects each, and after application of our eligibility criteria, between 44 and 48 eligible subjects per site remained. Reasons for ineligibility included subject's death prior to discharge and in-hospital stroke.

Subjects enrolled in the MOS appeared to be largely similar to the subjects enrolled in the MASCOTS registry prior to the start of the MOS (Table 2). No statistically significant differences were found by sex, race, smoking status, mRS, length of stay, nursing home residence, or past medical history of stroke, diabetes or heart disease. However, subjects in the follow-up study were significantly younger (mean 67 vs. 65), were more likely to have sustained an ischemic stroke, less likely to have sustained a TIA or HS, and more likely to be ambulatory upon discharge.

Subjects who completed the wave 1 interview were similar to those subjects who were enrolled in the MOS but did not complete the interview (Table 3). No statistically significant differences were found by sex, race, stroke subtype, past medical history of stroke, diabetes, hypertension, smoking status, nursing

home residence, ambulatory status pre-stroke and at discharge, mRS or length of stay. However, those who completed the interview were slightly older (mean 62 vs. 66) and more likely to have a history of heart disease.

Baseline characteristics of the MOS measured in hospital are presented in Table 4. Follow-up subjects ranged in age from 19 to 96, with a mean age of 64.7 years. Slightly more than half the subjects were 65 years or older. Nearly three-quarters of enrolled subjects were white; the remainder were mostly African Americans. Ischemic strokes were the most common subtype (74.3%), followed by TIA (13.9%) and HS (11.8%). Comorbidities in the past medical history included prior stroke/TIA (37%), diabetes (26.3%), heart disease (30.8%), and hypertension (66.5%). Twenty-six percent of subjects were smokers at the time of admission, and only 1.3% were nursing home residents. Prior to their stroke, most (95.4%) could ambulate independently. However, at discharge, only 69.8% were able to do so. Nearly half (46.2%) had mRS indicating moderate to severe disability at discharge. The majority of registry subjects (60.7%) stayed in the hospital five days or less.

Some sex differences were evident at baseline in unadjusted analyses (Table 4). Females were significantly older than males (mean 67 vs. 63), less likely to have a history of heart disease, and less likely to smoke. There was a marginally significantly greater prevalence of diabetes in females. A difference in stroke subtype was evident, with females being more likely to have TIA and less likely to have HS. Females and males did not differ significantly in terms of proportion completing the interview, race, past medical history of stroke or

hypertension, nursing home residence, ambulatory status pre-stroke or at discharge, mRS, or length of stay, or proportion discharged to a rehabilitation facility. The proportion of subjects requiring a proxy respondent did not differ significantly by sex.

The death certificate search confirmed that 13 subjects – 6 females and 7 males -- died before the 90 day interview (Table 5). Our overall 90-day case fatality rate (CFR), contingent on live discharge, was 3.5%. The CFRs for males and females were 4.3% and 2.9%, respectively. Nine of the deaths were among subjects whose index stroke was IS (3.2% of all IS), while 4 were among HS survivors (9% of all HS). Eight of the 13 decedents had a stroke-related underlying cause of death (UCOD). Of the remaining five subjects, two had a cardiac diagnosis listed as the UCOD, two listed cancer and one listed peripheral vascular disease.

Based on self-report from the follow-up interview, few sex differences in the utilization of medical services were evident (Table 6). Males and females did not differ significantly in terms of the proportions requiring of emergency hospitalizations for stroke-related, heart-related, or all reasons. However, a non-significantly larger proportion of women had emergency hospitalizations (17 vs. 12%, p=.21). Males and females used home health services during the post-discharge period at similar rates. There was no significant difference in the number of physician visits by sex. However, differences emerged in utilization of rehabilitation services. Females were significantly more likely to participate in

physical therapy (45% vs. 30%) and there was a trend toward more females undergoing speech therapy (19% vs. 12%).

Bivariate analyses of ADL independence revealed relationships with many baseline factors (Table 7). Overall, 155 subjects (56%) scored ≥95 on the BI indicating minimal limitations in ADL. There was a significant relationship with age, with older subjects less likely to achieve ADL independence (OR 0.94, 95% CI 0.95-0.98). Males were more than twice as likely as females to achieve a BI score of at least 95 (OR 2.26, 95% CI 1.36-3.38). There was a trend toward whites being more likely than non-whites to achieve ADL independence. As expected, subjects who had Modified Rankin Scores less than 3 at discharge were far more likely (OR 3.7, 95% CI 2.22-6.21) to achieve ADL independence at follow-up than subjects with Modified Rankin Scores ≥3. Similarly, ambulatory subjects, both pre-stroke and at discharge, were far more likely to report ADL independence than subjects who were unable to ambulate independently. Not unexpectedly, subjects with IS were half as likely to achieve ADL independence than subjects with TIA (OR 0.48, 95% CI 0.24-0.95), but surprisingly, subjects with HS did not differ significantly from subjects with TIA in odds of ADL independence (OR 1.25, 95% CI 0.43-3.63). Finally, as expected, subjects able to complete an interview themselves were far more likely than those requiring a proxy respondent to achieve ADL independence (OR 4.84, 95% CI 2.66-8.79).

Baseline characteristics were significantly related to SS-QOL domain and Summary Scores in the unadjusted bivariate analyses (Table 8). For all domains and the Summary Score, subjects who completed the interviews themselves had

higher (better) scores than subjects whose interviews were completed by proxy. Physical Function domain scores were statistically significantly associated with age, sex, race, mRS, ambulatory status pre-stroke and at discharge, and stroke subtype. Language domain scores were significantly associated with age, race, ambulatory status prestroke and at discharge, and stroke subtype. Whites had significantly higher Vision domain scores than non-whites. Thinking domain scores were statistically significantly higher among males. Energy domain scores were statistically significantly higher in males, whites, and subjects who were independently ambulatory at discharge. Mood domain scores were significantly associated with age, race, mRS, and ambulatory status at discharge. Role Function domain scores were statistically significantly higher in males, whites, subjects with lower mRS, subjects who were able to ambulate prestroke and at discharge, and cases of HS/TIA. Summary Scores were significantly associated with sex, race, mRS, ambulatory status pre-stroke and at discharge, and stroke subtype.

Results of the multivariable logistic regression analysis of ADL recovery are presented in Table 9. Adjusting for age, race, stroke subtype, prior stroke, interview source, and ambulatory status at discharge, males had nearly threefold greater likelihood of recovering in ADL at follow-up (OR 2.75, 95% CI 1.49-5.08). Because a non-significantly higher percentage of women than men reported emergency hospitalizations in the post-discharge period, we considered the possibility that these events could explain some of the observed sex differences in stroke recovery. Emergency hospitalizations for any reason prior to follow-up

were associated with a marginally significant halving of the odds of recovery (OR 0.46, 95% CI 0.20, 1.06). Adding these self-reported events to the baseline model did alter the sex difference in odds of recovery (OR 2.74, 95% CI 1.48-5.08).

Multiple linear regression models confirmed a significant independent effect of sex on SS-QOL domain and summary scores, with either significant main effects of sex or significant interactions with sex on all eight SS-QOL measures (Tables 10-11). Models for domains 1-4 (Physical Function, Language, Vision, and Thinking) are presented in Table 10. For Physical Function, baseline characteristics explained 38% of the variance in scores (i.e., R^2=.38), with significant main effects of sex, race, interview source, and ambulatory status at discharge. The model developed for Language explained 22% of the variance, with significant main effects of sex, age, race, and interview source. Baseline characteristics explained only 14% of the variance in Vision domain scores, with significant main effects of race and interview source, and a significant interaction between sex and diabetes. This interaction indicated statistically significantly higher Vision scores in men with diabetes, compared to women. For the Thinking domain, 11% of the variance was explained by the baseline model, which contained significant main effects of sex, age, and interview source.

Models for domains 5-7 (Energy, Mood, and Role Function) and the SS-QOL summary score are presented in Table 11. The baseline model explained only 15 percent of the variance in Energy domain scores, having significant main effects of sex, race, interview source, diabetes, and cardiac history. For the Mood

domain, the baseline model explained 25% of the variance, with significant main effects of age, interview soruce, and diabetes, and interactions of sex with interview source and prior stroke. Interactions with sex are described more fully with least-squares means below. The Role Function model explained 24% of the variance in that domain's scores, having significant main effects of interview source, ambulatory status at discharge, and diabetes, and an interaction between sex and stroke history. The baseline model explained 30% of the variance in the SS-QOL Summary Score, with significant main effects of age, race, interview source, and diabetes, and a significant interaction between sex and prior stroke.

The addition of emergency hospitalizations to the baseline models explained no more than 4% additional variance over the baseline model in any of the domains (Tables 10-11). These adverse health events did not confound the previously noted sex differences.

To provide an overall summary of the independent effect of sex on QOL, we generated least squares means for males and females (Table 12). Except when interactions with sex were present, males' scores are statistically significantly higher than females' scores. In the Vision domain, non-diabetic females had non-significantly higher scores than non-diabetic males, while diabetic males had significantly higher scores than diabetic females. In the Mood domain, females with a prior stroke had non-significantly higher scores than the corresponding males, while males without prior stroke had significantly higher scores than corresponding females. Females with proxy respondents had

marginally significantly higher Mood scores than males with proxy respondents, while male subjects scored significantly higher than female subjects. In the Role Function domain, scores for males and females with prior stroke did not differ significantly, although the mean female score was higher. Among subjects without prior stroke, males achieved significantly higher Role Function scores. Finally, males and females with prior stroke had very similar SS-QOL Summary Scores, while males scored significantly higher than females in the stratum without prior stroke.

To assess the influence of the inclusion of proxy respondents on our SS-QOL scores, we generated least square means for males and females from our baseline models excluding proxy respondents (Table 13). Overall, as expected, mean scores are higher without the inclusion of proxies. A loss of statistical significance occurred in the Vision domain among subjects with diabetes, with a decrease in the mean difference between males and females. Otherwise, in all other domains, the relationships between scores for males and females remained similar, with similar mean differences and statistical significance.

DISCUSSION

In this broadly inclusive cohort of stroke survivors from a hospital-based stroke registry in Michigan we found marked sex differences in ADL independence and across all measured domains of QOL. These differences are not explained by age at stroke occurrence, stroke subtype, or comorbidities. Our findings substantially agree with other recent reports of sex differences in stroke outcomes from other countries. However, this is the first report of stroke outcomes from a prototype of the Paul Coverdell National Acute Stroke Registry, and the first registry-based study to report scores of the Stroke-Specific Quality of Life scale.

Cohort Description

Compared to other stroke survival cohorts, the MOS is generally more inclusive because it was designed with the goal of generalizability to all stroke patients in Michigan. The MOS included all adults (≥18 years) with a full range of stroke subtypes, including TIA and SAH, recurrent strokes, subjects who would require proxy assistance to complete a follow-up interview, and subjects with significant impairments prior to the index stroke. The descriptive data demonstrated that the goals of the MOS were met – a broadly representative patient cohort was enrolled and followed up. We identified six comparable stroke follow-up studies that have reported results by sex. However, as expected there are potentially important differences between the MOS and these other studies noted as follows. The Kansas City Stroke Registry is the only comparable study from the United States. It enrolled 459 subjects from several health care facilities

in one metropolitan area, limited to subjects aged at least 50 years, included prior strokes only if there was no residual deficit, excluded TIA and SAH, and excluded subjects where were not independent in ADL before their stroke and subjects with various comorbidities [12, 26, 30, 31]. The Registry of the Canadian Stroke Network enrolled over 3000 subjects, primarily from tertiary care institutions [9, 32]. Riks-Stroke, an ongoing Swedish national stroke quality of care registry, excluded TIA and SAH [8, 14, 15]. The Northeast Melbourne Stroke Incidence Study (NEMESIS), another population-based study, excluded TIA and SAH, and excluded recurrent stroke survivors from follow-up studies [16]. The European BIOMED Stroke Project excluded subjects with prior stroke or TIA [7, 13]. A large cohort population-based study using data from administrative databases in Ontario excluded both TIA and SAH cases [6]. Proxy respondents were included in both the European BIOMED study and NEMESIS, although NEMESIS did not collect proxy information on mood. Proxy consent was obtained for the Canadian registry, reportedly resulting in a biased sample [33], although the use of proxy respondents is not specifically mentioned in a report on stroke outcomes [9]. Follow-up for the Swedish study was by mail, so respondents may have had assistance. Follow-up in the Ontario study was managed through administrative records rather than through patient contact, so no proxy respondents were required to obtain data on subjects with cognitive or communicative impairments. The Kansas City study did not report on subjects who were unable to complete follow-up interviews themselves.

Case Fatality

Only 13 MOS subjects died in the first three months, resulting in a 90-day CFR of 3.5% overall, 4.3% for males and 2.9% for females. This was not a statistically significant difference. Because the MOS only enrolled subjects who were alive at discharge, it is not possible to compare our rates with CFRs from other studies. A recent report based on National Health and Nutrition Examination Survey (NHANES) data from 1982-1992 found similar 28-day age-adjusted CFR after first-ever stroke for white men and women of approximately 16%. However, the same study found an apparent sex difference in CFR for blacks, with rates of 6.4% in men and 20.0% in women [34].A population-based study in Rochester, Minnesota documented survival after first cerebral infarction; after adjusting for age and other patient characteristics, they found no significant sex difference in survival, with overall survival of 83% after 1 month, and 77% after 6 months [35]. A large multi-country European study found no statistically significant differences in 3 month case fatality after adjusting for age and country [7]. A report from the Swedish stroke registry also found no differences between men and women in age-adjusted 90-day CFR. Finally, a Canadian population-based study using information from linked administrative databases did find sex differences in survival after stroke, but only in older age groups [6]. Specifically, men aged 75-84 had higher mortality at 30 days than women in the same age group, and men aged over 85 had higher mortality at both 30 days and 1 year than women over 85. It is clear that our overall 90-day CFR of 3.5% is very low, which is a consequence of enrolling only subjects alive at discharge. Future

analyses of MASCOTS registry data will determine whether sex differences exist for in-hospital deaths. In this small number of deaths, no sex difference in survival in the first three months after a stroke is suggested.

Activities of Daily Living

We hypothesized that women would lag behind men in achieving independence in activities of daily living (ADL) as measured by achieving a score of at least 95 on the BI at 3 months. In bivariate analysis, males had a twofold greater odds of achieving independence in ADL by the 3 month follow-up interview. After controlling for age, stroke subtype, prior stroke, functional status pre-stroke, race, and interview source, the male advantage increased to nearly threefold. Other studies have also found that females are more likely to lag behind males in ADL recovery after stroke. Analyzing data on 459 subjects from the Kansas City Stroke Study, Lai found that females were less likely to achieve a BI score of 95 by 6 months [12]. However, this difference was erased after controlling for post-stroke depression (PSD), age, stroke severity, and prestroke physical function. Adding PSD to the model assumes that depression is a confounder of the relationship between sex and ADL independence. Comparing models with and without post-stroke depression may instead indicate the proportion of ADL recovery that is mediated by depression. If both the greater prevalence of depression observed in females and the deficit in ADL recovery have the same cause – e.g., a severe stroke with wide-ranging effects on the brain – and if sex modifies the effect of the stroke's brain injury, then adjusting for depression in the relationship between sex and ADL recovery may mask an

important true difference in the consequences of stroke between the sexes. The European BIOMED study found that women were more likely to be disabled at 3 months, as defined by a BI score of 70 or less after adjusting for age and country [7]. Finally, in data from the Swedish registry, women were less likely to be independent in primary ADL (mobility, toilet visits, and dressing) at 3 month follow-up, as well as more likely to be institutionalized [8]. ADL independence is an important basic component of autonomy, and evidence is mounting that women are less likely to achieve this autonomy after a stroke. Because this difference is not explained by age or other known confounders, other factors such as sex-related differences in stroke characteristics [18], quality of care [36], or the social or physical environment may be involved [37], and should be the focus of further studies in this area.

Quality of Life

Quality of Life instruments aim to assess residual deficits in patients' perception of the impact of their health state on their overall life satisfaction. Only a few reports of QOL in stroke survivors based on disease-specific instruments are available in the literature.

The Stroke Impact Scale (SIS) was developed in the Kansas City Stroke Registry cohort. The instrument consists of 59 items that generate 8 domain scores: Strength, Hand Function, Mobility, ADL/instrumental ADL (IADL), Memory, Communication, Emotion, and Participation [31]. In addition, a composite Physical domain score can be calculated by combining four domains (Strength, Hand Function, ADL/IADL, Mobility), and a subset of 16 items can be

used to compute the SIS-16 physical function measure [38]. However, the SIS may not be used to generate a score for overall QOL, in contrast to the SS-QOL. In the Kansas City cohort, Duncan and colleagues used the SIS to demonstrate that, among stroke survivors who had achieved a BI score of ≥95, difficulties remained in Hand function, Participation (a measure of social role function), and Physical Function. However, no significant sex differences were found in that study [31].

No studies have assessed the comparability of SS-QOL and SIS scores. In some domains, the two scales appear to measure similar constructs (e.g. SS-QOL Physical Function vs. SIS-16, SS-QOL Language vs. SIS Communication), but the two instruments use somewhat different questions to assess these constructs.

To the best of our knowledge, no other published reports of SS-QOL version 3 results are available for comparison to our results. Furthermore, no reports of SS-QOL scores by sex are have been published. However, we have compared our mean SS-QOL scores by sex to overall mean scores calculated during the development of the SS-QOL instrument (Linda Williams, personal communication, 2006) as a general indicator of the performance of the SS-QOL in our sample. For all domains except Role Function, the SS-QOL development study's mean scores fell within the range we report for males and females, suggesting that the study populations are similar. For Role Function, our means for both males and females were somewhat lower than the SS-QOL development mean.

Our finding that males have statistically significantly higher adjusted Physical Function domain scores than females (4.2 vs. 3.9) is not surprising in light of the large difference in the odds of ADL recovery we found. Other studies have also found higher scores for males on physical function measures from other instruments. For example, in the Kansas City Stroke Study, females were less likely to score at least 90 points on the SF-36 Physical Functioning scale [12]. Researchers from the Registry of the Canadian Stroke Network reported significantly lower median SIS-16 composite physical function scores for women than men, which roughly corresponds to a half-point difference in mRS scores [9]. While these differences between men and women may not be clinically significant on an individual patient level, but they do suggest that women, overall, experience somewhat less satisfaction with their level of Physical Functioning after a stroke than men.

In our study, women had significantly lower adjusted mean Language scores than men (4.3 vs. 4.5), indicating that women feel they have more trouble understanding others and being understood. Two studies reported that women were more likely to present with aphasia at stroke onset (Roquer 2003, Di Carlo 2003). Another study reporting various functional scores by gender found no objective differences in speech quality, auditory comprehension, or language during in the early weeks after a stroke or after one year [39]. It is unclear whether the sex difference in SS-QOL Language scores signal clinically significant or objective differences in language functioning, such as residual aphasia, or whether they reflect differing expectations in males and females.

The SS-QOL Vision questions assess whether subjects have difficulty doing particular things, such as watching television or reaching for things, because of difficulty seeing. In the Vision domain, we found a significant interaction between sex and past medical history of diabetes, with diabetic males having significantly higher adjusted vision scores than diabetic females (4.74 vs. 4.37), and no significant difference among non-diabetics (4.58 vs. 4.71). While there are biological reasons why diabetics should have more vision problems than non-diabetics, the reasons for a gender difference in the effect of diabetes on subjective assessment of visual difficulties are not obvious.

The SS-QOL Thinking domain assesses whether the subject experiences difficulty with concentration and memory. In the MOS, the sex difference in the Thinking domain is relatively large (3.38 vs. 2.78 for males and females, respectively). A study assessing objective cognitive differences in stroke survivors found that women actually performed better than men on memory tasks [40] . In our study, women are clearly bothered more by difficulties with concentration and memory. As with any QOL domain, subjects' self-assessment of thinking ability could be colored by depression. Furthermore, among depressed subjects, real deficits in memory and mental processing may be present.

The Energy domain reflects subjective feelings of tiredness and the need to rest. In our study, men's adjusted Energy scores are nearly half a point higher than women's scores (2.99 vs. 2.53). Follow-up data from the Swedish study indicated that, two years after a stroke, women are more likely than men to report

that they are often or always tired [17]. The sex difference in energy scores could also reflect somatic symptoms of depression.

The Mood domain of the SS-QOL measures depressive feelings. In our study, prior stroke, interview source, and stroke subtype all interacted with sex in this outcome. Depending on the strata examined, our scores for males range from 2.59-4.02, while scores for females range from 3.06-4.19. Females had statistically significantly lower mood scores (i.e., more depressive feelings) than men among the sub-group with no prior stroke history and among patient interviews. However, the interaction with interview source in particular raises concern about the validity of proxy Mood scores, as female proxies had higher scores than male proxies, while female patients had lower scores than male patients. These scores may be biased due to gender differences in the proxy respondents -- this issue is further explored below. Although the SS-QOL Mood domain is not a clinically validated depression scale, the significantly lower Mood scores for female patients echo findings from many other studies. Females experience more depressive symptoms after stroke than males [41-43], are more likely to self-report depression after a stroke than males [14], and have more clinically diagnosed major depression than males among subjects with no stroke history [44]. Depression has far-reaching consequences for health: studies have found that post-stroke depression may hinder functional recovery [12, 42, 45], and depressive symptoms in stroke-free adults are associated with an increased risk of stroke mortality [41]. A tendency toward depressive affect would likely influence patients' perceptions about their QOL in other areas, and could be one

of the causes of the lower QOL scores for females in other domains and in the overall score. We did not collect an independent measure of depression, so we have not attempted to adjust QOL scores in other domains for depressive symptoms.

The Role Function domain attempts to measure whether the subject participates in social and family activities to the degree desired. Our results suggest that Role Function is, not surprisingly, a complex construct that has many contributing factors, including diabetes, smoking status, and multiple interactions with age and sex. We found that Role Function scores differed by sex only among subjects who had not had a prior stroke (2.91 vs. 3.45 for females and males, respectively). This finding could reflect a short-term sex difference in adaptation among first-ever stroke patients that is not evident after stroke recurrence. The interaction of interview source with sex could be a function of systematically different characteristics of the proxies for males and females. For example, because males are younger on average, they may more often have a spouse serving as proxy than females, who, being older, may more often have a son or daughter as caregiver. We believe that proxy responses in the more qualitative domains such as this one should be interpreted with caution.

Other cohort studies have reported on the effects of sex on overall quality of life using various generic QOL instruments. In a large Australian inception cohort study, the Assessment of Quality of Life (AQoL) instrument was administered to stroke survivors. In that study, women had AQoL scores nearly half those of males two years post-stroke. The Registry of the Canadian Stroke

Network found no difference in Health Utilities Index scores for men and women at 6 months post-stroke [9]. We are unaware of other cohort studies that provide measures of overall quality of life, without subdivision into Mental and Physical Components Scores (as in the commonly used SF-36 and its derivatives). The SS-QOL Summary Score, a stroke-specific measure of overall QOL, is simply an unweighted mean of an individual's scores in all 7 domains. It is therefore not surprising that patterns of sex differences evident in the individual domains also appear in the Summary Score. Summary scores are lower for females than males, at least among subject interviews (3.65 vs. 4.02) and among subjects without prior stroke (3.54 vs. 3.98).

Considering the SS-QOL least-squares means for domain and Summary Scores as a whole, it is apparent that, even after adjusting for age and other potential confounders, female stroke survivors in the MOS feel less satisfied with their functioning in many areas.

Medical Services and Past Medical History

Quality of life at follow-up may be affected by interactions with the health care system during the recovery period. Our analysis of self-reported medical services utilization determined that 50% more females received physical therapy than males. This result was somewhat surprising, given that females were not more likely to be non-ambulatory at discharge or to have higher (poorer) modified Rankin scores. We did not consider physical therapy in our follow-up multivariable models because of the likelihood of confounding by indication; that is, the physical therapy would be associated with poorer QOL and lower odds of

ADL recovery because subjects more affected by their strokes would be more likely to be referred for therapy. The greater deficits in physical function among females at follow-up, as evidenced by lower scores on the SS-QOL Physical Function domain and a lower proportion achieving ADL independence, persisted in spite of these services. This finding may indicate that females need even more, or more effective, physical rehabilitation services, or that other factors such as depression are limiting the effectiveness of the therapy. Females had non-significantly more emergency hospitalizations in the post-stroke months than males (17% vs. 12%), perhaps as a result of their greater age, but adding these events into the baseline models did not alter the relationship of sex to the outcomes measured.

In order to consider the potential confounding effects of past medical history on quality of life, we analyzed several past medical history variables by sex. A few sex differences were evident in our sample. We found a trend toward more females than males having diabetes mellitus. The European BIOMED Stroke Project found no sex difference in diabetes prevalence among stroke survivors [13], while a large Canadian administrative database study found slightly higher prevalence of diabetes in male stroke patients [6]. Other studies have found more hypertension among females than males with stroke [9, 46] and our data demonstrate a trend in that direction. As expected, we found that more males smoke and have histories of myocardial infarction and/or coronary heart disease. Finally, a non-significantly larger proportion of women had a history of stroke or TIA.

Past medical history information was found to be a significant predictor in a few of the multivariable models. Prior stroke was, not surprisingly, an important predictor of failure to achieve independence in ADL. It also played an important role in Mood, Role Function, and Summary Score through interaction effects. Neither hypertension nor smoking were significant predictors of QOL in multivariable models, nor did they confound the relationship between sex and QOL. Diabetes was associated with several QOL domains, but not ADL recovery. A history of heart disease had a significant negative effect on Energy scores.

Potential for Selection Bias

To assess the representativeness of our follow-up study with respect to the state-wide registry sample, we compared the subset of registry subjects who would have been eligible for the follow-up study to the 373 MOS subjects who consented to follow-up. These registry subjects were enrolled prior to the start of the follow-up study at each site, and were limited to only those hospitals that participated in the follow-up study. For this comparison, registry subjects also had to have been discharged alive. Subjects enrolled in the MOS follow-up study were significantly younger, and were significantly more likely to be ambulatory at discharge than subjects in the MASCOTS registry. These characteristics likely reflect the eligibility criteria used in the MOS which excluded subjects with poor patient prognosis. MOS subjects also had a different case mix, having a larger proportion of IS and a smaller proportion of TIA. Because subjects had to be approached for consent while in hospital, TIA patients, who would typically have short stays, would have had less opportunity to be approached and consented.

The MOS and the original MASCOTS registry were very similar in terms of sex distribution as well as most potential confounders of the sex-stroke outcome relationship. We believe that because we controlled for age, functional status, and stroke subtype in our analyses, our outcomes results have a high degree of internal validity and are generalizable to strokes in Michigan and elsewhere.

We were able to interview 75% of enrolled survivors in our registry. The potential for non-response bias must therefore also be addressed. The major causes of non-response were refusal (12%) and loss to follow-up (11%). Those who completed the interview were significantly older than those who were not interviewed and had significantly more heart disease in their medical histories. The age difference may reflect greater difficulty in contacting younger subjects who may have returned to work and be more mobile. Combined with the larger percentage of TIA among subjects who did not complete the interview, these differences may suggest that subjects who have fewer lingering effects from their strokes may have had less interest in participating in the follow-up survey. The differences in cardiac history are likely a function of the greater age of the interview participants. Overall, males have a greater proportion of cardiac diagnoses, although males were not over-represented in the outcomes study. We were encouraged by the strong similarities between participants and non-participants in most other measured characteristics that relate directly to their strokes or stroke risk, especially the similar proportions of ambulatory subjects, subjects with high modified Rankin scores, and subjects who smoke or have a history of hypertension, diabetes, or prior stroke. It is therefore unlikely that the

follow-up study is sufficiently biased to negatively affect the validity of our findings regarding the effect of sex on stroke outcome.

Proxy Assessments

Our finding that 25% of stroke survivors required proxy assistance to complete the telephone interview is similar to rates of proxy use from other stroke studies [16, 47]. Because our goal was to assess the burden of stroke across its entire spectrum, we were committed to collecting outcomes data from all stroke survivors, ranging from TIA patients with no residual effects to subjects who were sufficiently impaired to be unable to complete a follow-up telephone interview. The use of proxy respondents may introduce bias, whereby proxy respondents rate the subject's health lower than the subject would rate their own health [48]. Proxy information for the Barthel Index, which requires observations of what the subject actually does, has been shown to be valid [22]. The validity of proxy information is of particular concern in areas of subjective feeling, such as Mood and Role Function. In a proxy validation study for the SS-QOL, proxies rated patients "slightly worse" than patients rated themselves in all domains except Role Function [49]. Proxy agreement was modest for Physical Function, with an intraclass correlation coefficient (ICC) of 0.5, and worse in other more subjective domains, such as Thinking and Role Function, with ICC as low as 0.3 [49]. Proxy validation studies of outcomes instruments require that included subjects be able to participate by themselves in order to provide a basis for comparison with the proxy response. Therefore, proxy validation studies are not necessarily generalizable to subjects who truly need a proxy's help [50]. In circumstances

where a proxy respondent is required, the proxy may actually be more highly attuned to the thoughts and feelings of the subject, and may provide more valid information than that obtained by proxies in a proxy validation study. On the other hand, it is expected that subjects who need a proxy truly do have more difficulties in many domains of QOL, and would be expected to have lower scores. We believe that accepting some proxy-related bias is preferable to the certain bias of a survival cohort that excludes the most affected subjects.

We assessed the effect of proxy responses on our conclusions in several ways. First, we performed bivariate analyses on our outcomes by proxy status. As expected, proxy status was significantly associated with poorer outcome (Table 7, 8). For the SS-QOL domains, proxy SS-QOL scores ranged from .4 points lower (Thinking) to 1.0 point lower (Physical Function). In a proxy validation study, Williams and coworkers found that proxy respondents had the greatest disparities from patient respondents in the Mood, Energy, and Thinking domains, with mean proxy scores 0.5 points lower in those domains [51]. In the MOS, raw patient and proxy scores in these domains differed by 0.8, 0.6, and 0.5, respectively. Next, we included interview source as a variable in our models to control for confounding that may arise if proxy status is also associated with the exposure. Because proxy consent was sought at enrollment, it is essentially a baseline characteristic like the other covariates in our models. Although not statistically significant, there was a surprising trend toward a larger proportion of males than females requiring proxy interviews (77% vs. 71%) (Table 4). This difference would be expected to lower scores for males relative to scores for

females, yet females' scores are significantly lower than males' in most domains. The type of information obtained from proxies for male and female respondents, and within other subgroups, may differ because of systematic differences in the relationship of the proxy to the subject. Therefore, we also considered interactions of other variables with interview source to assess whether proxy status operates differently in subgroups of subjects. In every model, proxy status emerged as either a significant main effect or interaction term. An interaction between sex and interview source were observed in the Mood domain, resulting in higher scores for males than females among patients, but marginally significantly higher scores for females than males among proxies. One interpretation of this interaction is that females with proxy respondents truly have better outcomes in this area than males with similar needs; however, it could also suggest differences in the caregivers. Williams found that certain characteristics of caregivers, such as depression and caregiver burden, were related to the validity of SS-QOL scores [49]. If these characteristics differ according to the sex of the subject, they could cause systematic differences for male and female subjects requiring proxy assistance. Unfortunately, we did not collect information about the proxy respondents themselves, so we were unable to control for proxy factors that may affect the validity of their responses. Finally, we performed a sensitivity analysis to assess the influence of proxy responses on our conclusions regarding sex and QOL by calculating least square means from our baseline models excluding proxy scores. Although mean scores are higher overall, the mean differences between adjusted male and female scores were

largely unchanged. Therefore, we conclude that the inclusion of information derived from proxy respondents has not compromised the internal validity of our QOL analyses.

Limitations

We did not collect prospective data on several factors that could influence recovery. In many cases, the lack of this information reflects the particular focus of the MASCOTS registry, which was on quality improvement, rather than to determine disease etiology or the long-term impact of stroke. We were not able to collect data on stroke severity (such as an NIH Stroke Scale) on the majority of our patients. We also did not employ a stroke classification scheme beyond the Coverdell stroke subtypes (such as TOAST criteria or Oxfordshire Community Stroke Project criteria). If sex differences exist in stroke severity or subtype, these may confound the relationship between sex and outcome. Marital status, income, education, and social support may have profound effects on adjustment to life after stroke [37, 52-54]. These factors may differ by sex and may explain some differences in recovery and quality of life. We have collected information on these factors in our 2-year follow-up interviews, and future analyses may shed light in this area. Other than pre-stroke ambulatory status, we did not collect detailed retrospective information on pre-stroke functional status or QOL; having information such as a pre-stroke BI or generic QOL measure would help us determine to what extent the index stroke has contributed to the outcomes measured at follow-up.

It is probable that subjects at different ages have different expectations for functioning and recovery, and these are reflected in the amount of difficulty perceived and reported for various tasks. Our female subjects were, on average, older than the males, but sex differences in stroke outcome persisted after adjustment for age. We were concerned about the possibility of residual confounding which could occur if we did not specify the correct relationship of age to ADL and QOL. We considered higher order age terms (age^2 and age^3), log(age), and age categories, as well as interactions of age with other covariates in the models. While some of these models fit the data better than the model with age as a linear, continuous variable, they did not alter the sex differences observed. We concluded that none of the alternatives controlled for confounding better than age alone. However, it is possible that the true relationship of age to QOL scores is nonlinear, resulting in inadequate adjustment for age in our models. A larger sample size or examination of these issues in a restricted age range could help identify the best approach to age adjustment.

Sex differences in our outcomes persisted after including self-reported emergency hospitalizations in the baseline models. We have not been able to examine the validity of the self-reported health care utilization information in the MOS because we do not have an independent source of data, such as follow-up hospital or physician's office records.

We were not able to control for symptoms at stroke onset. The particular symptom profile may provide important clues as to severity and outcome. If symptoms differ by sex, as some authors have found [18, 46], they may help

explain some of the differences in outcomes seen in this study, either through delays in care or biological differences in stroke's effects. We plan to examine symptoms in future analyses of the MASCOTS registry data set.

We were also limited by a small sample size. For the wave 1 analysis, the 270 respondents allowed us to determine that statistically significant sex differences exist in health-related QOL and odds of ADL recovery in our cohort. However, small numbers of subjects precluded considering certain information in our models, such as potential differences in outcome between ICH and SAH. Additional attrition in successive waves of data collection may limit our power to observe similar differences, if they exist, after additional follow-up.

We acknowledge that the large number of statistical tests performed on our data set may have resulted in some spurious chance findings. However, the general consistency in the findings relating to our primary exposure of interest give us confidence that sex differences in stroke recovery are a reality.

Areas for Future Research

The current report has addressed sex differences in stroke outcome in our wave 1 follow-up interviews, begun 3 months post-stroke. We will report outcomes from the wave 2 and 3 interviews, conducted at 1 year and 2 years post-stroke, in the future. In addition, analyses of the larger full MASCOTS registry data with respect to sex similarities and differences in quality of care, diagnostic procedures, interventions, and medication use will enhance our understanding of how men and women with stroke interact with the health care system.

Few methodological studies have been conducted on the SS-QOL instrument itself. It was designed to be an evaluative instrument, with the capacity to detect meaningful change in individuals over time. We plan to conduct analyses of factors influencing individuals' change over time in the MOS cohort using mixed model analyses. In addition, using data from our study, we plan to examine responsiveness of the instrument to changes in QOL measured through global questions regarding overall HRQOL similar to those used by Williams in validating the SS-QOL[25].

Data on stroke outcomes from unselected populations in the United States are scarce. More studies that assess stroke survivors in both subjective and objective measures are needed to determine whether and to what degree sex differences in outcome exist. If, as we found, differences in important outcomes such as quality of life and ADL recovery persist that are not explained by the higher average age of female patients, reasons for these differences should be found and addressed.

APPENDIX A: TABLES

Table 1. Summary of stroke outcome measures

Rating Scale	Construct Measured	Score Range	Validity	Reliability	Ceiling/Floor Effects
Modified Rankin Scale (MRS)	Activity limitations and participation restrictions	6 grades: 0 (no symptoms) to 5 (requires constant care)	Content: Limited to mobility and continence. Construct: Correlates with BI and NIH Stroke Scale.	κ ranges from .3-.8 [19]. Discrepancies noted in middle grades [20]	No/No
Barthel Index (BI)	ADL limitations	0 (completely dependent in ADL) to 100 (completely independent), in 5-point increments	Often used as a criterion measure of ADL.	High interrater reliability; may be reliably administered by patient or a proxy [22].	Yes/No
Stroke-Specific Quality of Life, v.3 (SS-QOL)	Disease-specific quality of life across 7 domains	0-5 for each domain and summary score	Content: Excellent [29]. Telephone administration valid [27].	Good test-retest reliability [27].	Not available*

Abbreviations: NIH=National Institutes of Health, ADL=Activities of Daily Living

*Work completed but not yet published (Linda Williams, personal communication)

Table 2. Comparison between subjects from MASCOTS registry with subjects from MOS follow-up study

	MASCOTS[a]		MOS		
	N	(%)	N	%	P-Value[b]
All Subjects	1318	(100.0)	373	(100.0)	
Gender					
Male	607	(46.1)	163	(43.7)	0.42
Female	711	(54.0)	210	(56.3)	
Age					
<65	516	(39.2)	173	(46.4)	0.01
≥65	802	(60.9)	200	(53.6)	
Mean Age (SD)	67.4	(15.6)	64.7	(14.9)	
Race					
Black	254	(19.3)	77	(20.6)	0.19
White	932	(70.7)	270	(72.4)	
Other/No Data	132	(10.0)	26	(7.0)	
Coverdell Stroke Subtype					
IS	830	(63.0)	277	(74.3)	<.001
HS	226	(17.2)	44	(11.8)	
TIA	262	(19.9)	52	(13.9)	
Past Medical History					
Prior Stroke/TIA/VBI	448	(34.0)	138	(37.0)	0.28
Diabetes Mellitus	357	(27.1)	98	(26.3)	0.75
Cardiac History (MI/CHD)	400	(30.4)	115	(30.8)	0.86
Hypertension	904	(68.6)	248	(66.5)	0.44
Community Dwelling	1278	(97.0)	368	(98.7)	0.07
Current Smoker	328	(24.9)	97	(26.0)	0.66
Ambulatory Status Pre-stroke					
Ambulatory	1175	(89.2)	347	(93.3)	
Ambulatory with assistance	42	(3.2)	7	(1.9)	0.11
Unable to ambulate	29	(2.2)	8	(2.1)	
Unknown	72	(5.5)	11	(3.0)	
Ambulatory Status at Discharge					
Independent	817	(62.0)	256	(68.6)	
Dependent	258	(19.6)	82	(22.0)	<.001
Unable to ambulate	186	(14.1)	29	(7.8)	
Unknown	57	(4.3)	6	(1.6)	
MRS at Discharge					
0-2	696	(52.8)	198	(53.1)	0.62
3-5	577	(43.8)	166	(44.5)	
Unknown	45	(3.4)	9	(2.4)	
Length of Stay					
≤5 days	808	(61.7)	225	(60.3)	0.62
>5 days	501	(38.3)	148	(39.7)	

[a] MASCOTS subjects limited to those discharged alive from the hospitals participating in the follow-up study prior to the start of enrollment for the MOS.

[b] P-value from χ^2 test

Table 3. Comparison between subjects who completed vs. did not complete wave 1 interview

	Complete		Not Complete		P-Value[a]
	N	(%)	N	(%)	
Total	270	(72.3)	103	(27.6)	
Sex					
Male	112	(68.7)	51	(49.5)	0.16
Female	158	(75.2)	52	(50.5)	
Age					
<65	117	(43.3)	56	(54.4)	0.06
≥65	153	(56.7)	47	(45.6)	
Mean Age (SD)	65.7	(14.6)	62.3	(15.5)	
Race					
Black	53	(19.6)	24	(23.3)	0.83
White	203	(75.2)	67	(65.1)	
Other/No Data	14	(5.2)	12	(11.7)	
Coverdell Stroke Subtype					
IS	202	(74.8)	75	(72.8)	0.15
HS	27	(10.0)	17	(16.5)	
TIA	41	(15.2)	11	(10.7)	
Past Medical History					
Prior Stroke/TIA/VBI	104	(38.5)	34	(33.0)	0.32
Diabetes Mellitus	73	(27.0)	25	(24.3)	0.59
Cardiac History (MI/CHD)	94	(34.8)	21	(10.4)	<.01
Hypertension	178	(65.9)	70	(68.0)	0.71
Community Dwelling	267	(98.9)	101	(98.1)	0.53
Current Smoker	68	(25.2)	29	(28.2)	0.56
Ambulatory Status Pre-stroke					
Independent	251	(95.4)	96	(97.0)	0.77[b]
Dependent	12	(4.6)	3	(3.0)	
Ambulatory Status at Discharge					
Independent	185	(69.8)	71	(69.6)	0.97
Dependent	80	(30.2)	31	(30.4)	
MRS at Discharge					
0-2	141	(53.8)	57	(55.9)	0.72
3-5	121	(46.2)	45	(44.1)	
Length of Stay					
≤5 days	164	(60.7)	61	(59.2)	0.79
>5 days	106	(39.3)	42	(40.8)	

[a] P-value from χ^2 test, except [b] P-value from Fisher's exact text

Table 4. Baseline characteristics of MOS subjects by sex

	All Subjects N	(%)	Male N	(%)	Female N	(%)	P-Value[a]
Total	373	(100.0)	163	(43.7)	210	(56.3)	
Follow-up Experience							
Died	15	(4.0)	9	(5.5)	6	(1.6)	
Refused	46	(12.3)	18	(11.0)	28	(13.3)	0.13
Lost to Follow-up	42	(11.2)	24	(14.7)	18	(8.6)	
Completed	270	(72.3)	112	(68.7)	158	(75.2)	
Age							
<65	173	(46.4)	89	(54.6)	84	(40.0)	0.005
≥65	200	(53.6)	74	(45.4)	126	(60.0)	
Mean Age (SD)	64.7	(14.9)	62.5	(15.2)	66.5	(14.6)	
Race							
Black	77	(20.6)	35	(21.5)	42	(20.0)	0.94
White	270	(72.4)	117	(71.8)	153	(72.9)	
Other/No Data	26	(7.0)	11	(6.8)	15	(7.1)	
Coverdell Stroke Subtype							
IS	277	(74.3)	124	(76.1)	153	(72.9)	0.03
HS	44	(11.8)	24	(14.7)	20	(9.5)	
TIA	52	(13.9)	15	(9.2)	37	(17.6)	
Past Medical History							
Prior Stroke/TIA/VBI	138	(37.0)	55	(33.7)	83	(39.5)	0.25
Diabetes Mellitus	98	(26.3)	35	(21.5)	63	(30.0)	0.06
Cardiac History (MI/CHD)	115	(30.8)	62	(38.0)	53	(25.2)	<.01
Hypertension	248	(66.5)	103	(63.2)	145	(69.1)	0.23
Current Smoker	97	(26.0)	53	(32.5)	44	(21.0)	0.01
Community Dwelling Pre-stroke	368	(98.7)	162	(99.4)	206	(98.1)	0.28
Ambulatory Status Pre-stroke							
Independent	251	(95.4)	154	(97.0)	193	(95.1)	0.40
Dependent	12	(4.6)	5	(3.1)	10	(4.9)	
Ambulatory Status at Discharge							
Independent	185	(69.8)	117	(73.1)	139	(67.2)	0.22
Dependent	80	(30.2)	43	(26.9)	68	(32.9)	
MRS at Discharge							
0-2	141	(53.8)	88	(55.0)	110	(54.9)	0.84
3-5	121	(46.2)	72	(45.0)	94	(46.1)	
Discharged to Rehabilitation	78	(28.9)	30	(26.8)	48	(30.4)	0.52
Length of Stay							
≤5 days	164	(60.7)	95	(58.3)	130	(61.9)	0.48
>5 days	106	(39.3)	68	(41.7)	80	(38.1)	
Interview Type (completed interviews only)							0.28
Patient	202	(74.8)	80	(71.4)	122	(77.2)	
Proxy	68	(25.2)	32	(28.6)	36	(22.8)	

[a] P-value from χ^2 test

Table 5: Death certificate information obtained on 13 deaths occurring during the 90 day post-discharge period

Stroke Subtype	Underlying cause of death	Related Causes: Stroke-related	Related Causes: Heart-related	Days survived after event	Sex
IS	Cerebral Infarction			25	female
IS	Stroke NOS			19	female
IS	Stroke NOS			8	female
IS	Stroke NOS			92	male
IS	Endocarditis	no	yes	40	female
IS	Ischemic Heart Disease	no	yes	18	male
IS	Brain Cancer	no	no	65	male
IS	Lung Cancer	no	no	88	female
IS	Other Peripheral Vascular Diseases	no	yes	93	male
HS (ICH)	Intracerebral Hemorrhage			76	male
HS (SAH)	Other non-traumatic intra-cranial hemorrhage			75	male
HS (SAH)	Stroke NOS			8	female
HS (SAH)	SAH			46	male

Table 6. Health care utilization post-discharge

	All Subjects N	%	Male N	%	Female N	%	P-Value[a]
All Subjects	270	(100)	112	(41)	158	(59)	
Emergency Hospitalizations							
Stroke-related	19	(7)	5	(4)	14	(9)	0.16
Heart-related	6	(2)	3	(3)	3	(2)	1.00[b]
Any reason	40	(15)	13	(12)	27	(17)	0.21
Rehabilitation Services							
Physical Therapy	105	(39)	34	(30)	71	(45)	0.02
Occupational Therapy	47	(17)	22	(20)	25	(16)	0.41
Speech Therapy	43	(16)	13	(12)	30	(19)	0.10
Home Health Services							
Registered Nurse	22	(8)	8	(7)	14	(9)	0.61
Home Health Aide	10	(4)	3	(1)	7	(4)	0.53[b]
Housekeeping	3	(1)	0	(0)	3	(2)	0.27[b]
Meals on Wheels	6	(2)	2	(2)	4	(3)	1.00[b]
Visits to Physician							
None	14	(5)	7	(6)	7	(4)	
Once	36	(13)	19	(17)	17	(11)	0.40
2-5	156	(58)	60	(54)	96	(61)	
6 or more	62	(23)	25	(22)	37	(23)	

[a] P-value from χ^2 test, except [b] P-value from Fisher's exact text

Table 7: Descriptive statistics and bivariate odds ratios for ADL independence (BI≥95) at 90 days

Mean (SD)	N	BI (%≥95)	OR (95% CI) [a]
All Subjects	270	57.4	
Age Group			
<50	42	73.8	
50-59	46	58.7	
60-69	62	67.7	0.94 [b] (0.95 - 0.98)
70-79	69	60.9	
≥80	51	25.5	
Sex			
Male	112	68.8	2.26 (1.36 – 3.38)
Female	158	49.4	1.00
Race			
White	202	60.6	1.7 (0.95 - 3.02)
Nonwhite	53	47.2	1.00
Modified Rankin Score			
0-2	141	71.6	3.7 (2.22 – 6.21)
3-5	121	40.5	1.00
Ambulatory status pre-stroke			
Independent	251	60.2	6.8 (1.44 – 32.11)
Dependent	11	18.2	1.00
Ambulatory status at discharge			
Ambulatory	185	66	3.23 (1.87 – 5.57)
Dependent	80	37.5	1.00
Coverdell Stroke Subtype			
IS	202	51.5	0.48 (0.24 – 0.95)
HS	27	74.1	1.25 (0.43 – 3.63)
TIA	41	75.6	1.00
Interview Type			
Subject	202	66.8	4.84 (2.66 – 8.79)
Proxy	68	29.4	1.00

Abbreviations: OR=odds ratio, CI=confidence interval

[a] Unadjusted odds ratios from logistic regression.

[b] Age modeled as a continuous variable; OR represents change in odds for a 1 year increase in age.

Table 8. Unadjusted bivariate mean SS-QOL scores at 90 days

	N	PF	L	V	Th	E	M	RF	SS
Age Group		*	*						
<50	42	4.1	4.0	4.5	2.8	2.7	3.2	2.8	3.5
50-59	46	4.2	4.4	4.7	3.1	2.8	3.6	3.1	3.7
60-69	62	4.3	4.5	4.7	3.2	2.9	3.8	3.4	3.8
70-79	69	4.0	4.4	4.6	3.0	2.6	3.6	2.9	3.6
≥80	51	3.5	4.4	4.5	3.0	2.6	3.6	2.7	3.5
Sex		*			*	*		*	*
Male	112	4.2	4.5	4.6	3.4	3.0	3.7	3.2	3.8
Female	158	3.9	4.3	4.6	2.8	2.5	3.5	2.9	3.5
Race		*	*	*		*	*	*	*
White	203	4.1	4.5	4.7	3.1	2.8	3.6	3.1	3.7
Other	61	3.7	4.1	4.3	2.9	2.3	3.3	2.7	3.3
Modified Rankin Score		*	*				*	*	*
0-2	141	4.3	4.5	4.7	3.1	2.9	3.7	3.3	3.8
3-5	121	3.6	4.2	4.5	2.9	2.6	3.4	2.6	3.4
Ambulatory status prestroke		*	*					*	*
Independent	251	4.1	4.4	4.6	3.0	2.8	3.6	3.0	3.7
Dependent	11	3.1	3.9	4.5	2.8	2.0	2.8	2.2	3.0
Ambulatory status at discharge		*	*			*	*	*	*
Independent	185	4.2	4.4	4.7	3.1	2.8	3.7	3.2	3.7
Dependent	63	3.5	4.2	4.5	2.8	2.5	3.3	2.6	3.4
Stroke Subtype		*	*					*	*
IS	202	4.5	4.7	4.8	3.3	2.8	3.8	3.3	3.9
HS	27	3.9	4.3	4.6	3.0	2.7	3.5	2.9	3.5
TIA	41	4.4	4.7	4.8	3.2	2.9	3.8	3.3	3.9
Interview Source		*	*	*	*	*	*	*	*
Subject	202	4.3	4.5	4.7	3.2	2.9	3.8	3.2	3.8
Proxy	68	3.3	3.9	4.3	2.7	2.3	3.0	2.4	3.1

*p<.05 for appropriate statistical test: Age: linear regression overall F-test; Other variables: student's t-test.

Abbreviations: PF=Domain 1: Physical Function, L=Domain 2: Language, V=Domain 3: Vision, Th=Domain 4: Thinking, E=Domain 5: Energy, M=Domain 6: Mood, RF=Domain 7: Role Function, SS=Summary Score

Table 9. Unadjusted and adjusted odds of ADL independence (BI≥95) at 90 days

Effect	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Baseline model		
Age	0.94[b] (0.95 - 0.98)	0.98 (0.96 - 1.00)
Race		
White	1.70 (0.95 - 3.02)	1.90 (0.95 - 3.81)
Nonwhite	1.00	1.00
Sex		
Male	2.26 (1.36 – 3.38)	2.75 (1.49 - 5.08)
Female	1.00	1.00
Stroke Subtype		
IS	0.48 (0.24 – 0.95)	0.89 (0.39 - 2.02)
HS	1.25 (0.43 – 3.63)	1.81 (0.50 - 6.53)
TIA	1.00	1.00
Prior stroke		
Present	0.42 (0.25 - 0.69)	0.48 (0.26 - 0.87)
Absent	1.00	1.00
Interview source		
Subject	4.84 (2.66 – 8.79)	4.72 (2.23 - 10.00)
Proxy	1.00	1.00
Ambulatory status at discharge		
Independent	3.23 (1.87 – 5.57)	2.29 (1.19 - 4.41)
Dependent	1.00	1.00
Baseline plus follow-up events model[b]		
Sex		
Male	2.26 (1.36 – 3.38)	2.74 (1.48 - 5.08)
Female	1.00	1.00
Emergency hospitalizations		
One or more	0.44 (0.22 - 0.87)	0.46 (0.20 - 1.06)
None	1.00	1.00

NOTE: OR=Odds Ratio, CI=Confidence Interval

[a]Odds ratios and 95% confidence interval from multiple logistic regression model

[b]Adjusted for all other variables in table

Table 10. Multiple linear regression models of the effect of baseline variables and follow-up emergency hospitalizations on SS-QOL, domains 1-4

Parameter	Category	1: Physical Function			2: Language			3: Vision			4: Thinking		
		β	(SE)	P	β	SE	P	β	SE	P	β	SE	P
Intercept		3.14	(0.34)	<0.0001	2.88	(0.28)	<.0001	4.20	(0.27)	<.0.0001	1.71	(0.46)	<0.001
Sex	Male	0.23	(0.10)	0.03	0.20	(0.09	0.02	-0.11	(0.10)	0.24	0.60	(0.15)	<0.0001
	Female	-	-	-	-	-	-	-	-	-	-	-	-
Age	per 10-year increase	-0.04	(0.04)	0.26	0.12	(0.03)	<0.001	0.004	(0.03)	0.89	0.10	(0.05)	<0.05
Race	White	0.36	(0.12)	<0.01	0.28	(0.11)	<0.01	0.35	(0.10)	<0.001	0.02	(0.17)	0.87
	Nonwhite	-	-	-	-	-	-	-	-	-	-	-	-
Stroke Subtype	IS	-0.09	(0.14)	0.52	-0.19	(0.12)	0.12	-0.09	(0.11)	0.41	-0.16	(0.20)	0.44
	HS	0.37	(0.21)	0.08	0.30	(0.18)	0.09	0.09	(0.17)	0.60	0.18	(0.29)	0.54
	TIA	-	-	-	-	-	-	-	-	-	-	-	-
Interview source	Patient	0.84	(0.13)	<0.0001	0.67	(0.11)	<0.0001	0.36	(0.10)	<0.001	0.60	(0.18)	<0.001
	Proxy	-	-	-	-	-	-	-	-	-	-	-	-
Ambulatory status at discharge	Independent	0.40	(0.12)	<0.001	-	-	-	-	-	-	-	-	-
	Dependent	-	-	-	-	-	-	-	-	-	-	-	-
Diabetes mellitus	Present	-0.40	(0.12)	<0.001	-	-	-	-0.32	(0.12)	<0.01	-	-	-
	Absent	-	-	-	-	-	-	-	-	-	-	-	-
Sex*Diabetes		-	-	-	-	-	-	0.47	(0.19)	0.01	-	-	-
R-squared		0.35			0.22			0.14			0.11		
Follow-up model: alterations to estimates for sex after ED-based hospitalizations added to above baseline model													
Sex	Male	0.21	(0.10)	0.03	0.20	(0.09)	0.02	-0.11	(0.10)	0.24	0.57	(0.14)	<0.0001
	Female	-	-	-	-	-	-	-	-	-	-	-	-
Sex*Diabetes		-	-	-	-	-	-	0.48	(0.19)	0.01	-	-	-
R-squared		0.38	-	-	0.23	-	-	0.14	-	-	0.15	-	-

Parameter estimates (β), standard errors (SE), and p-values (P) from multivariable linear regression, adjusted for all variables with an estimate reported.

Table 11. Multiple linear regression models of the effect of baseline variables and follow-up emergency hospitalizations on SS-QOL domains 5-7 and Summary Score

Parameter	Category	5: Energy		6: Mood		7: Role Function		Summary Score	
		β SE	P	β SE	P	β SE	P	β SE	P
Intercept		2.01 (0.51)	<0.001	1.27 (0.53)	0.02	1.63 (0.49)	0.001	2.53 (0.29)	<0.0001
Sex	male	0.48 (0.17)	<0.01	-0.20 (0.27)	0.45	0.59 (0.18)	<0.01	0.46 (0.18)	0.08
	female	- -	-	- -	-	- -	-	- -	-
Age	per 10-year increase	0.001 (0.06)	0.98	0.19 (0.05)	<0.0001	0.06 (0.05)	0.26	0.07 (0.03)	0.03
Race	white	0.47 (0.19)	0.02	0.17 (0.15)	0.28	0.32 (0.17)	0.06	0.28 (0.01)	<0.01
	non-white	- -	-	- -	-	- -	-	- -	-
Stroke Subtype	IS	0.11 (0.22)	0.6	0.03 (0.18)	0.87	-0.06 (0.20)	0.78	-0.04 (0.12)	0.72
	HS	-0.11 (0.32)	0.75	0.27 (0.26)	0.29	0.08 (0.29)	0.78	0.09 (0.18)	0.61
	TIA	- -	-	- -	-	- -	-	- -	-
Interview Source	subject	0.50 (0.20)	0.01	0.58 (0.20)	<0.01	0.74 (0.18)	<0.0001	0.64 (0.14)	<0.0001
	proxy	- -	-	- -	-	- -	-	- -	-
Ambulatory status prestroke	independent	- -	-	0.53 (0.31)	0.09	- -	-	- -	-
	dependent	- -	-	- -	-	- -	-	- -	-
Ambulatory status at discharge	independent	- -	-	- -	-	0.37 (0.17)	0.03	- -	-
	dependent	- -	-	- -	-	- -	-	- -	-
Prior stroke	present			-0.09 (0.17)	0.6	-0.08 (0.19)	0.66	-0.09 (0.11)	0.45
	absent	- -	-	- -	-	- -	-	- -	-
Diabetes mellitus	present	-0.58 (0.18)	<0.01	-0.35 (0.14)	0.02	-0.57 (0.16)	<0.001	-0.36 (0.10)	<0.01
	absent	- -	-	- -	-	- -	-	- -	-
Cardiac history	present	-0.44 (0.18)	0.01	- -	-	- -	-	- -	-
	absent	- -	-	- -	-	- -	-	- -	-
Sex*Interview source		- -	-	0.80 (0.29)	<0.01	- -	-	- -	-
Sex*prior stroke		- -	-	-0.58 (0.27)	0.03	-0.82 (0.30)	<0.01	-0.50 (0.18)	<0.01
R-squared		0.15		0.25		0.24		0.29	
Follow-up model: alterations to estimates for sex after ED-based hospitalizations added to above baseline model									
Sex	male	0.47 (0.16)	0.04	-0.22 (0.27)	0.42	0.58 (0.18)	<0.01	0.45 (0.11)	<0.0001
	female	- -	-	- -	-	- -	-	- -	-
Sex*Interview source		- -	-	0.82 (0.29)	<0.01	- -	-	- -	-
Sex*Prior stroke		- -	-	-0.58 (0.27)	0.03	-0.81 (0.30)	<0.01	-0.49 (0.18)	<0.01
R-squared		0.15		0.25		0.25		0.31	

Parameter estimates (β), standard errors (SE), and p-values (P) from multivariable linear regression

Table 12: Least-squares means by sex

Domain	Interaction	Female	Male	P-value*
1. Physical Function		3.92	4.15	0.03
2. Language		4.28	4.48	0.02
3. Vision	With Diabetes	4.38	4.73	0.03
	Without Diabetes	4.71	4.59	0.24
4. Thinking		2.78	3.38	<0.0001
5. Energy		2.52	3.01	<0.01
6. Mood	With Prior Stroke	3.44	3.26	0.40
	Without Prior Stroke	3.53	3.93	0.01
	Proxy Interview	3.05	2.63	0.09
	Patient Interview	3.63	4.00	0.01
7. Role Function	With Prior Stroke	2.81	2.58	0.33
	Without Prior Stroke	2.89	3.48	<0.01
Summary Score	With Prior Stroke	3.45	3.41	0.78
	Without Prior Stroke	3.53	3.99	<0.0001

*Stratum-specific P-value for male vs. female comparison

Table 13: Least-squares means by sex, proxy responses excluded

Domain	Interaction	Female	Male	P-value*
1. Physical Function		4.16	4.41	0.03
2. Language		4.44	4.59	0.06
3. Vision	With Diabetes	4.48	4.75	0.13
	Without Diabetes	4.75	4.73	0.83
4. Thinking		2.92	3.49	0.001
5. Energy		2.61	3.21	<0.01
6. Mood	With Prior Stroke	3.51	3.49	0.92
	Without Prior Stroke	3.65	4.28	<0.001
	Patient Interview**	3.60	3.98	<0.01
7. Role Function	With Prior Stroke	2.97	2.79	0.51
	Without Prior Stroke	3.03	3.82	<0.001
Summary Score	With Prior Stroke	3.61	3.56	0.73
	Without Prior Stroke	3.66	4.23	<0.0001

*Stratum-specific P-value for male vs. female comparison
**Because of the exclusion of proxy responses from this analysis, the overall adjusted mean is presented for comparison with patient means in table 11.

APPENDIX B: FIGURES

Figure 1. Relationship of sex to stroke and stroke outcome, adapted from the World Health Organization's framework for the International Classification of Functioning, Disability, and Health (ICF).

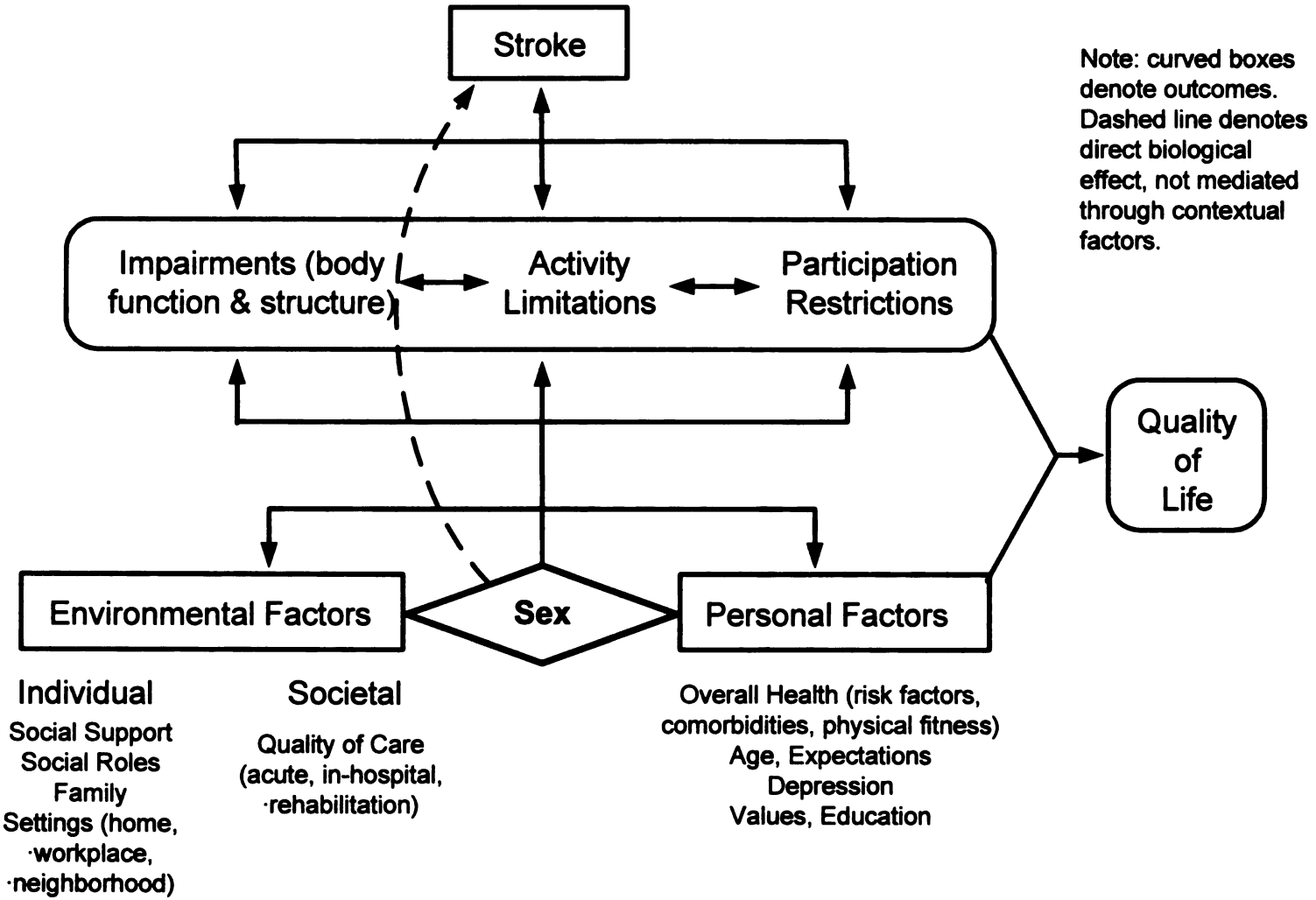


Figure 2. MASCOTS Registry and MASCOTS Outcomes Study

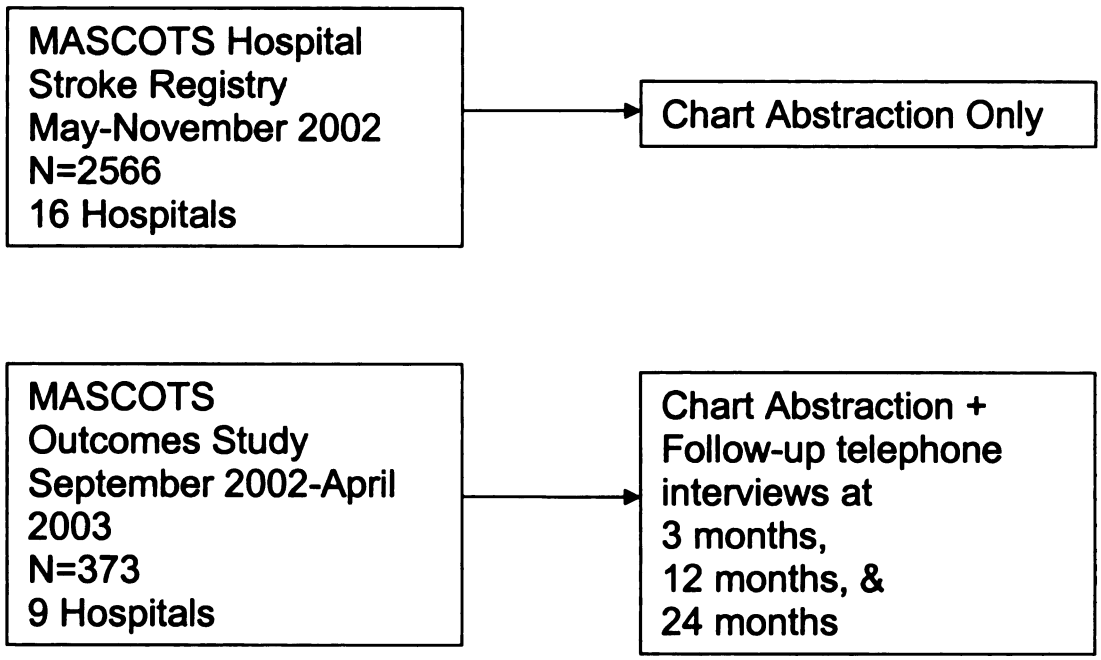
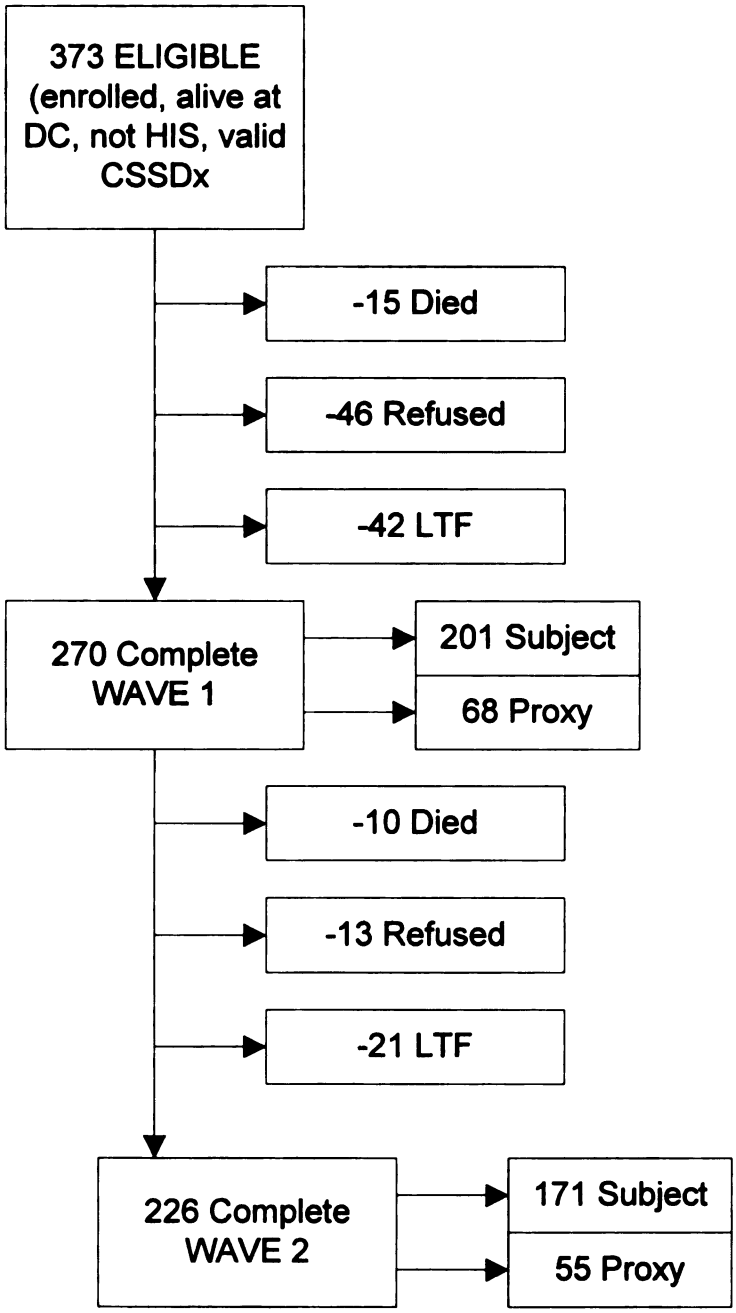


Figure 3: Flow of subjects through the MASCOTS Outcomes Study



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