Sex differences in post-stroke aphasia rates are caused by age. A meta-analysis and database query

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Abstract

Background: Studies have suggested that aphasia rates are different in men and women following stroke. One hypothesis says that men have more lateralized language function than women. Given unilateral stroke, this would lead to a prediction of men having higher aphasia rates than women. Another line of observations suggest that women are more severely affected by stroke, which could lead to a higher aphasia rate. An additional potential confounding variable could be age at stroke, given that women are typically older at the time of stroke.

Methods & Procedures: This study consists of two parts. First, a meta-analysis of the available reports of aphasia rates in the two sexes was conducted. A comprehensive literature search yielded 25 studies with sufficient aphasia and gender information. These studies included a total of 48,362 stroke patients for which aphasia rates were calculated. Second, data were analyzed from an American health database with 1,655,295 stroke patients, in order to include age and stroke severity into a regression analysis of sex differences in aphasia rates.

Outcomes & Results: Both analyses revealed significantly larger aphasia rates in women than in men. This speaks against the idea that men should be more lateralized in their language function. Furthermore, when age and stroke severity were included as covariates, sex failed to explain any aphasia rate sex difference above and beyond that which is explained by age differences at time of stroke.

Introduction

A stroke is a medical condition in which blood flow to the brain is restricted, due to occlusion (ischemic stroke) or haemorrhage (haemorrhagic stroke), resulting in cell death (WHO). In the US alone, approximately 800,000 people experience a stroke each year, according to the American Heart Association [1]. Stroke is the leading cause of motor and cognitive disability in western countries and aphasia, the inability to comprehend and formulate language because of brain damage, is one of the most common deficits after stroke. A large variability in the reported frequency of aphasia can be found in the literature [e.g. 2, 3-5], ranging from 15 to 68 percent of acute patients. A recent meta-analysis, however, concluded that aphasia is present in approximately 30 % of acute patients and 34 % in rehabilitation settings [6].

The variability of measured prevalence of aphasia has many causes. The method for aphasia identification differs between hospitals and countries and some sub-scores for aphasia in stroke scales have been found to be limited in their accuracy and reliability [7, 8]. The meta-analysis also did not take sex differences into account.

Stroke affects the sexes differently. Stroke is more common among men [9]. The symptoms of stroke have also been found to differ somewhat between men and women. Women are often more severely affected overall, more often experience paralysis, impaired consciousness and altered mental status together with a generalized weakness, while men more often experience dysarthria, diplopia, sensory loss, ataxia and balancing problems [10]. An association between pre-stroke dementia, which is more prevalent in women, and stroke severity has also been noted [11]. Aphasia following stroke has also been reported to affect women to a larger degree than men [see 10 for a review], although evidence has been conflicting [e.g. 12, 13, 14].

Sex differences in certain linguistic domains are also known to exist within the normal population, with differences in first language acquisition speed [15] and reading and writing abilities [16] being the most consistent, favoring girls/women over boys/men. Differences in word use have also been documented [17]. The underlying causes for these differences are probably complex and research trying to tie them to brain structure and function has yielded inconsistent results [18].

Some studies have argued for the hypothesis that language is more bilaterally organized in the brains of women than in men [e.g. 19, 20-22], although this is highly controversial [18, 23, 24]. A sex difference in language lateralization would ultimately lead to a sex difference in aphasia following unilateral stroke. If men's language is more lateralized in the brain than women's, we would expect them to be more prone to aphasia following unilateral stroke and vice versa, if women have greater language lateralization than men, we would expect their language function to be more vulnerable to stroke.

In this paper I conduct a meta-analysis on aphasia prevalence given stroke for the two sexes across published papers and compare it to data from a large American patient database (Healthcare Cost and Utilization Project (HCUP) under Agency for Healthcare Research and Quality, U.S. Department of Health & Human Services: https://hcupnet.ahrq.gov). Given that both analyses are based on fully anonymized and publicly available data, the study poses no ethical concerns.

Meta-analysis methods

A pub-med search including the terms “stroke” AND “aphasia” AND “gender” (which is a more inclusive term that includes “sex”) generated 211 citations in June 2018 (see Fig 1 for a flow-chart of the data sampling procedure). References in review articles on stroke and aphasia were also investigated. A total of 419 titles were considered. 90 papers were selected for further inspection on the basis of their title and abstract. The analysis set out to study post-stroke aphasia in the broadest sense. Speech pathology test still lack standardization and diagnostic data for identifying aphasia in stroke populations [25]. Different diagnostic approaches to aphasia were therefore not distinguished. All studies including some overall aphasia diagnosis were deemed relevant. Inclusion criteria were the following: 1) Primary peer reviewed studies reporting aphasia prevalence among stroke patients; 2) Studies reporting overall number of aphasia patients from a unselected stroke cohort, i.e. studies including only sub-types of aphasia were excluded and studies of group comparisons between aphasia patients and matched control groups were also not considered; 3) Reports reporting aphasia counts for both male and female aphasia patients as well as for stroke patients or where these could be extracted from reported percentages; 4) First/Primary report of data: The same data could only be included once. If more than one paper investigated the same patient group, the earliest/most comprehensive publication was chosen.

Fig 1. Data gathering flow-chart. Flow chart depicting the different phases of data gathering.

Twenty-five studies were included in the final dataset [4, 5, 11-14, 26-44]. One study [12] contained information about aphasia prevalence for different age bands. These groups were included separately (see Table 1 and Fig 2).

Table 1. Studies included in the meta-analysis

Study	Place	Note	N(stroke)	Aphasia Rate (Female)	Aphasia Rate (Male)	Ratio	95% CI lower	95% CI upper
Brust et al. 1976	New York, USA	acute stroke	850	18.4	23.8	0.774	0.580	1.040
Siirtola et al. 1977	Turku, Finland	acute stroke	338	28.7	28.2	1.016	0.670	1.540
Miceli et al. 1981	Rome, Italy	223 CVA, 128 tumours, 29 traumas etc	390	60.8	62.3	0.975	0.750	1.280
Scarpa et al. 1987	Modena, Italy	left hemisphere stroke, post 14 days	196	62.5	50.0	1.250	0.860	1.820
Hier et al. 1994	four sites, USA	acute stroke	1805	22.6	19.4	1.103	0.920	1.330
Pedersen et al. 1995	Copenhagen, Denmark	acute stroke	881	39.7	34.8	1.140	0.920	1.420
Laska et al. 2001	Danderyd, Sweden	acute stroke	106	33.3	34.7	0.961	0.500	1.850
Godefroy et al. 2002	Lille, France	Acute stroke, Aphasia	308	68.5	66.1	1.037	0.790	1.360
Di Carlo et al. 2003	7 European countries	acute stroke	4499	34.8	30.3	1.337	1.060	1.690
Kelly-Hayes et al. 2003	Framingham MA, USA	at 6 months post stroke	108	23.8	11.6	2.143	0.780	5.900
Roquer et al. 2003	Barcelona, Spain	acute stroke	1581	28.9	21.6	1.335	1.100	1.630
Engelter et al. 2006	Basel, Switzerland	acute ischemic stroke	269	34.0	23.9	1.422	0.890	2.260
Kyrozis et al. 2009	Acadia, Greece	28 days post-stroke	555	27.6	18.8	1.473	1.040	2.090
Tsouli et al. 2009	Athens, Greece	acute stroke	2297	41.3	31.5	1.313	1.140	1.510
Brkic et al. 2009	Tuzla, Bosnia and Herzegovina	acute stroke	993	23.0	17.6	1.309	0.990	1.730
Bersano et al. 2009a, <64 years	seven regions, Italy	acute stroke, <64 years	1751	21.0	20.0	1.044	0.840	1.300
Bersano et al. 2009b, 64-74 years	seven regions, Italy	acute stroke, 64-74 years	2663	26.0	24.0	1.081	0.930	1.260
Bersano et al. 2009c, 75-84 years	seven regions, Italy	acute stroke, 75-84 years	2853	31.0	27.0	1.160	1.010	1.330
Bersano et al. 2009d, >84 years	seven regions, Italy	acute stroke, 84< years	1581	43.0	35.0	1.223	1.030	1.450
Dickey et al. 2010	Ontario, Canada	at discharge	15327	33.4	31.0	1.078	1.020	1.140
Gall et al. 2010	Melbourne, Australia	acute stroke, Dysphasia	843	46.1	35.6	1.294	1.040	1.600
Gialanella et al. 2011	Lumezzane, Italy	acute stroke	262	55.9	44.4	1.258	0.890	1.770
Croquelois & Bogousslavsky 2011	Lausanne, Switzerland	acute stroke	5880	28.1	24.9	1.128	1.020	1.250
Jerath et al. 2011	Rochester, USA	acute stroke	449	45.8	37.4	1.222	0.910	1.640
Kadojic et al. 2012	Osijek, Croatia	acute ischemic stroke	177	48.2	37.2	1.294	0.820	2.040
Flowers et al. 2013	Toronto, Canada	acute ischemic stroke	221	35.7	26.0	1.373	0.850	2.220
Wasserman et al. 2015	Ottawa, Canada	isolated aphasia as only deficit of stroke	1155	4.1	3.0	1.347	0.720	2.510
Chang et al. 2015	Colombo, Sri Lanka	data from questionnaire	24	62.5	56.2	1.111	0.370	3.320
ALL			**48362**	**29.6**	**26.0**	**1.139**	**1.100**	**1.180**

Overview of the studies included in the meta-analysis on sex differences in post-stroke aphasia rate.

Fig 2. Meta-analysis forest plot. Forest plot of aphasia rate male/female ratios for the 25 studies included in the meta-analysis (total n=48,362), showing that across studies a small but significant effect of sex exists, indicating that women are more likely to get aphasia from stroke. This effect, however, does not take age or stroke severity into account.

Below, I report the excluded full-text papers (see Fig 1). This is done in order to give the reader a complete overview of the selection process. As mentioned, studies were included on the basis of the overall number of stroke patients being available for calculation of prevalence. I excluded reviews [6, 9, 10, 45-52], studies with insufficient information about sex [2, 53-85], studies with insufficient aphasia information [86-91], studies with insufficiently specified sampling procedure for aphasia patients from stroke cohorts [92-105], and studies with repetition of data use [37].

Results of meta-analysis

The 25 studies included a total of 48,362 stroke patients (23,085 women, 25,297 men). Of these 13,398 (6,828 women, 6,570 men) were diagnosed with aphasia (27.7%). 29.6 % of female stroke patients were diagnosed, while 26 % of males were diagnosed with aphasia (see Table 1 and Fig 2). This difference was found to be statistically significant using a paired and weighted t-test on the aphasia rates across studies, weighted to add emphasis on studies with larger patient samples, $t(27)=6.76$, $p<0.001$, forcing a rejection of the null-hypothesis that there is no difference in aphasia rate between women and men. The overall sex aphasia rate ratio was found to be 1.14 (1.10-1.18 95% CI) with a Cohen's *d* of 0.37 which is usually considered a small effect [106].

A funnel plot did not suggest any outspoken bias in the reports (see Fig 3). Including publication year as a covariate in a regression analysis did not alter the result and was not in itself a significant predictor of sex differences.

Fig 3. Funnel plot. A Funnel plot did not indicate any outspoken bias in the meta-analysis data.

Interim discussion

A higher aphasia rate after stroke for women than for men was found across studies in the meta-analysis. The average aphasia rate for women was 29.6% and for men 26% (see Table 1). The effect-size was in the small range.

The aphasia rate across studies and sexes (27.7%) was comparable to that reported in a recent meta-analysis (30%) [6]. The slightly lower estimate may in part be related to the inclusion of a study of cases with isolated aphasia [41] which had a much smaller aphasia rate than studies with a regular aphasia diagnosis (see Table 1). The aphasia rate ratio for the sexes reported by [41], however, was comparable to that of most other studies in the sample. Study year did not explain any variance in sex differences, suggesting that e.g. evolving diagnostic procedures for aphasia [25] has not had a major impact on sex differences in aphasia rates. Fig 2 displays publication year on the y-axis, and given that there had been changes as a function of time, this should be visible as either a leftward or rightward trend in the data points. This seems not to be the case.

The fact that a higher aphasia rate after stroke for women than for men is found across studies in the meta-analysis contradicts the notion that language in men is more lateralized than in

women (see introduction). If men have more lateralized language, one would expect their language to be more vulnerable to unilateral stroke than women's language, which, as shown, is not the case. But the findings are also at odds with previous critical suggestions that there are no sex differences in language lateralization between women and men [e.g. see 18, 107]. At face value, the findings would suggest that women in fact have more lateralized language than men. There are, however, reasons to hesitate before arriving at such a conclusion, based on the present analysis. As mentioned in the introduction, stroke is known to affect men and women differently on a number of accounts, including general severity. The sexes also differ on general health levels, resulting in women being older, on average, when they get a stroke [9]. Age has previously been found to be a predictor of acquiring aphasia [51]. In order to investigate if the effects of sex found in the meta-analysis are specific to language or may relate to more general differences that are unlikely to be caused by a sex difference in core language function, an investigation of aphasia rates that include additional explanatory variables is needed. Unfortunately, very few studies in the current cohort make detailed, reports of age effects on aphasia stratified for sex. One exception is Bersano et al. [12] who report aphasia rates for 4 different age groups. Here an interaction between age and sex differences seemingly can be observed. The sex difference is almost non-existing in the youngest age group (under 64), but gradually grows larger and larger in older age groups. It thus seems that taking age into account is important when trying to understand the sex difference in aphasia rates.

Another possible explanation for the higher aphasia rate in women is that they may be affected more severely by stroke in a non-discriminant manner [10]. If aphasia rates can be explained by severity alone, it would again suggest that the sex difference is not restricted or

related to language in any meaningful way. But again, this type of information is not reported in the papers covered by the present meta-analysis.

I have therefore added a 2nd dataset from an American healthcare database (see below) that will allow me to investigate aphasia rates while taking age and stroke severity into account.

Methods for database analysis

Data from the Healthcare Cost and Utilization Project (HCUP) from community hospitals in the United States were used for the analysis. The database (https://hcupnet.ahrq.gov/) contains inpatient diagnostic information using the International Classification of Diseases and Health Related Problems (ICD-9) codes from 35 US American states from the years 2011-2014. The ICD system is used by US hospitals for reimbursement purposes and subsequent research, e.g. to study patterns and outcome of disease [108]. Patient numbers from each year for each state, stratified by sex, was used in the analysis. Data from this database has previously been used to study post-stroke aphasia rates [2], but here we add sex as an explanatory variable and incorporate all available states for all the years in which the ICD-9 diagnoses were used (i.e. 10 times more patients).

To identify number of patients with stroke, the combined number of diagnoses from the database related to stroke was obtained. Cases with the following IDC-9 codes were included: “434.00 Crbl Thrmbs Wo Infrct”, “434.01 Crbl Thrmbs W Infrct”, “434.10 Crbl Emblsm Wo Infrct”, “434.11 Crbl Emblsm W Infrct”, “434.90 Crbl Art Oc Nos Wo Infrc”, “434.91 Crbl Art Ocl Nos W Infrc”, “436 Cva”. To identify the number of patients with aphasia, the IDC-9 code: “784.3 Aphasia” was used. As a proxy for stroke severity, the number of hemiparesis/hemiplegia diagnoses were included (using the IDC-9 code: “342.90 Unsp

Hemiplga Unspf Side", which is the most commonly used ICD-9 code for hemiplegia/paresis in the data). Hemiparesis, hemiplegia and aphasia are comorbid deficits. Around 90% of aphasia patients have hemiparesis [63], but if a sex difference in number of aphasias is accompanied by a similar sex difference in hemiparesis/hemiplegia diagnoses, then the difference is likely to be explained by stroke severity rather than being a specific language related phenomenon.

The database allows for two different ways to draw data. Either one can draw "Principal" diagnoses or "all-listed" diagnoses. As aphasia is often unlikely to be the principal diagnosis in a hospital visit, "all-listed" diagnoses were used. However, age information is only available with "principal" diagnoses, and age information was therefore drawn from this data. The assumption is that age differences in principal diagnosis will be representative for age differences in the "all-listed" diagnoses as well. It is important to note that the database does not offer information about age for any individual patient. These data are all summery data for the participating states for a particular year (2011-2014). Yet, similarly to a meta-analysis of data from different studies, summary data from different states, each representing a large group of patients may nevertheless be representative of generalizable differences between groups (males and females) in the data.

To evaluate statistical significance of these findings, a linear mixed-effects regression analysis was conducted, fit by REML, using the *lmertest* package in R [109]. P-values were estimated using Satterthwaite's method. The model incorporated aphasia rate as the dependent variable and sex as the main fixed dependent variable. Age and rate of hemiplegia diagnoses (proxy for stroke severity) were z-score scaled and added as additional covariates. The model also included all possible interactions between the three variables. US state and year for each data-

point were included as random effects. The regression was weighted by number of stroke cases in a particular state/year, to put more weight on data-points from larger states.

Results of database analysis

A total of 1,655,295 stroke patients were found in the database (863,612 women, 791,683 men) in the period from 2011 to 2014. Aphasia was diagnosed in 623,942 cases (336,604 women, 287,338 men) or 37.7%. Using this method, 38.9 % of female stroke patients were diagnosed, while 36.2 % of males were diagnosed with aphasia (see Fig 4).

Fig 4. **US data forest plot.** Aphasia rate ratios (uncorrected for age) for each US state in the HCUP database from 2011-2014. This analysis replicates the findings from the meta-analysis and provides unequivocal evidence for a higher aphasia rate among women compared to men given stroke (see Fig 1, but note the scale difference between plots). However, as Fig 5 shows, this effect can be explained completely by the sex difference in age at stroke.

The overall female/male aphasia rate ratio was found to be 1.073 (1.068-1.079 95% CI) with a Cohen's *d* effect size across states of 0.63 which is usually considered a medium effect size [106]. A paired t-test again yielded support to the existence of a sex difference, $t(143)=-13.74$, $p<0.001$.

When including age and stroke severity in a regression analysis, however, no significant effect of sex over and above that explained by age and severity could be observed, $t(272.33)=-0.826$, $p=0.4$. A significant effect of age, $t(275.23)=2.21$, $p(uncorrected)<0.05$, and a significant effect of stroke severity, $t(268.66)=5.34$, $p<0.001$ was observed. Fig 5 displays how sex is completely confounded by age of stroke and does not add any explanatory

power to the analysis. A significant interaction between age and stroke severity was also observed, $t(275.9)=-2.30$, *p(uncorrected)*<0.05. No other interactions were significant.

Fig 5. Aphasia rate as a function of age at stroke. A scatterplot of stroke average age against aphasia rate for each US state and year (2011-2014) in the HCUP database. The plot illustrates the large age difference between men and women at time of stroke. It also shows a positive correlation between average age and aphasia rate, suggesting that older stroke patients more often get aphasia. When this relationship is taken into account, sex effects are no longer significant in the aphasia rates.

Discussion

On this very large cohort of patients, we replicate the findings from the meta-analysis. Based on raw aphasia rates, women are more likely to get an aphasia diagnosis following stroke than men. The sizes of the effects vary somewhat across the two analyses. The aphasia ratio is smaller for the database study, but the effect size is found to be larger. This is likely due to the fact that the database data is more homogeneous than the data included in the meta-analysis, where the time of diagnosis post-stroke differs and also to some extent the definition of aphasia (e.g. one study includes dysphasia as well as aphasia and one study only looks at isolated aphasia cases – see Table 1 for details).

At the same time, our 2nd analysis completely revokes the conclusions that one could have drawn from the meta-analysis. In the database, we find no evidence of any sex difference in aphasia rates over and above that which can be explained by the age differences between females and males at time of stroke. This replicates previous findings that age is a predictor of aphasia following stroke [51], and given that age is a more fundamental causal variable than

language (i.e. your language cannot change your age, but the opposite may be true), it is likely that most if not all of the sex differences in aphasia rates is caused by the age difference in stroke between women and men.

We also find an independent effect of stroke severity on aphasia rates as measured by diagnoses of hemiplegia. Aphasia and hemiparesis/hemiplegia are known to be highly co-morbid. In this study we find that severity effects on aphasia are independent of the sex effects. The sex differences thus do not seem to be related to stroke severity per se. It has to be said, however, that this analysis uses a somewhat crude proxy for stroke severity. Other measures, such as general stroke scale scores [110, 111] might interact more with sex.

Bersano et al. [12] found indications of increasing sex differences in aphasia rates with age. Contrary to this, the database analysis shows no indication of an interaction between sex and age. Bersano and co-workers did not report inferential statistics documenting an actual interaction, but looking at their data, the increasing discrepancy in aphasia between males and females with age is striking. For patients below 64 years the aphasia rate gender ratio is 1.04 and grows to 1.08 in 64-74 year old patients, 1.16 in 75-84 and 1.22 in patients above 84 years of age (see Table 1). How does this fit with the current data not showing any interaction between age and sex? One possible explanation is that there is an inherent bias in the way that the Bersano and co-workers' age data is distributed. When lumping the data into 10 year age bins, one needs to take into account that women and men may not be equally distributed within each bin. The data from the Bersano et al. study were collected in 2001 in Italy. If one looks at the gender and age distribution of the Italian population in January 2002 using population statistics (http://demo.istat.it/pop2002/index_e.html), one finds that because women live longer than men, the average age of women within the different age bins from

middle age and onwards is higher than that of men and that this difference gets larger for the older groups. For the 54 to 64 year old Italians, the mean age difference between men and women is 0.07 years, but for the age group above 84 years, it has grown to 0.52 years. There is a very strong linear correlation between these mean age differences in the Italian population in these age bins and the reported differences in aphasia rate (r= 0.96, data available from author on request), which suggests that at least some of the interaction between gender and age reported by Bersano and co-workers is based on unequal sampling of the different ages. This is not to say that there could not be sex and age interactions that are not picked up by the current analysis. The data from the database is distributed on a state by year basis and each data-point for age is the result of averaging across many individual patients. Underneath this gross simplification may be hidden lots of interesting variability. Further studies are needed in order to rule out a potential interaction between sex, age and aphasia.

The present analyses are also limited in that they say nothing about the different types of aphasia symptoms that patients may suffer from and the potential interactions that might be found with gender if one looks more carefully at aphasia subtypes.

Taken together, the results are in line with a critical stance towards any large-scale brain base for sex differences in language [18]. This, of course, does not mean that the observed sex differences in language related behavior (see introduction) do not have brain correlates, just that these differences will be dynamic, complex and to a large extent dependent on gender differences in experience and context rather than being tied to genetic sex.

Conclusion

Women were found to be diagnosed with aphasia following stroke more often than men. This is in direct opposition to the hypothesis that women have less lateralized language function

than men. The gender difference is most likely caused by age differences in the two groups at the time of stroke.

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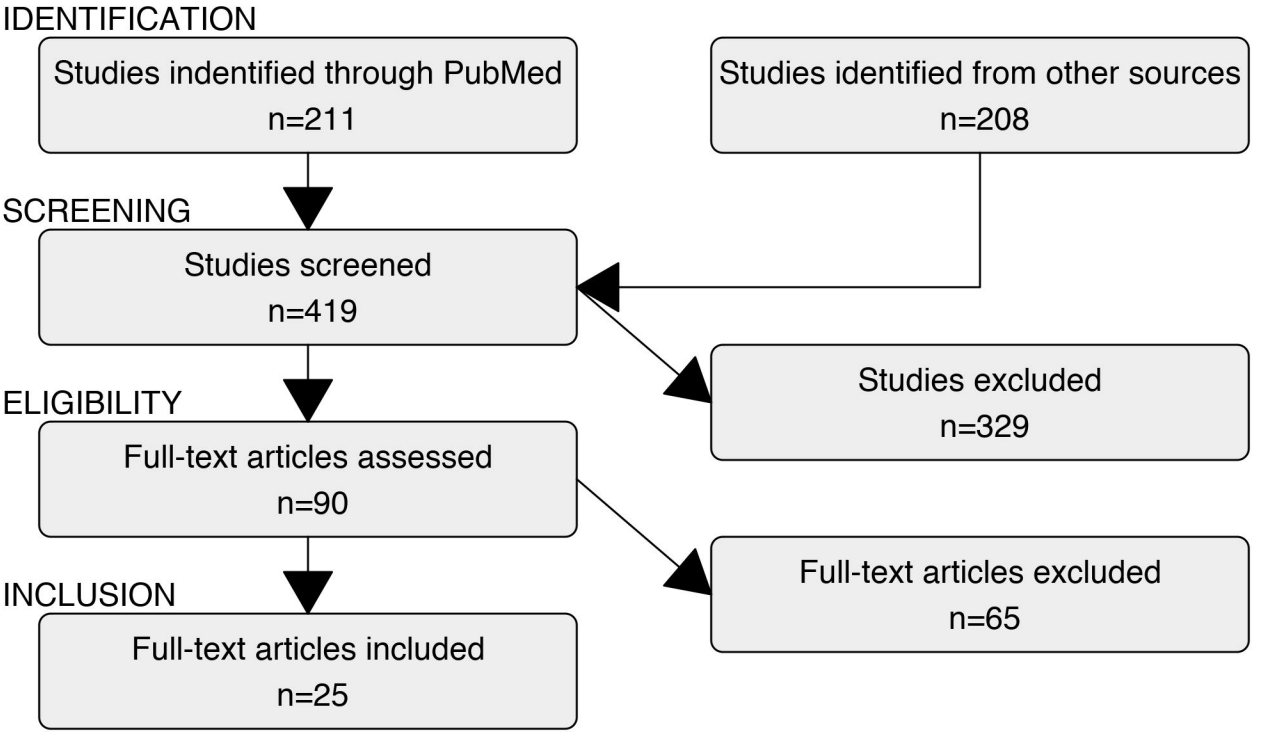
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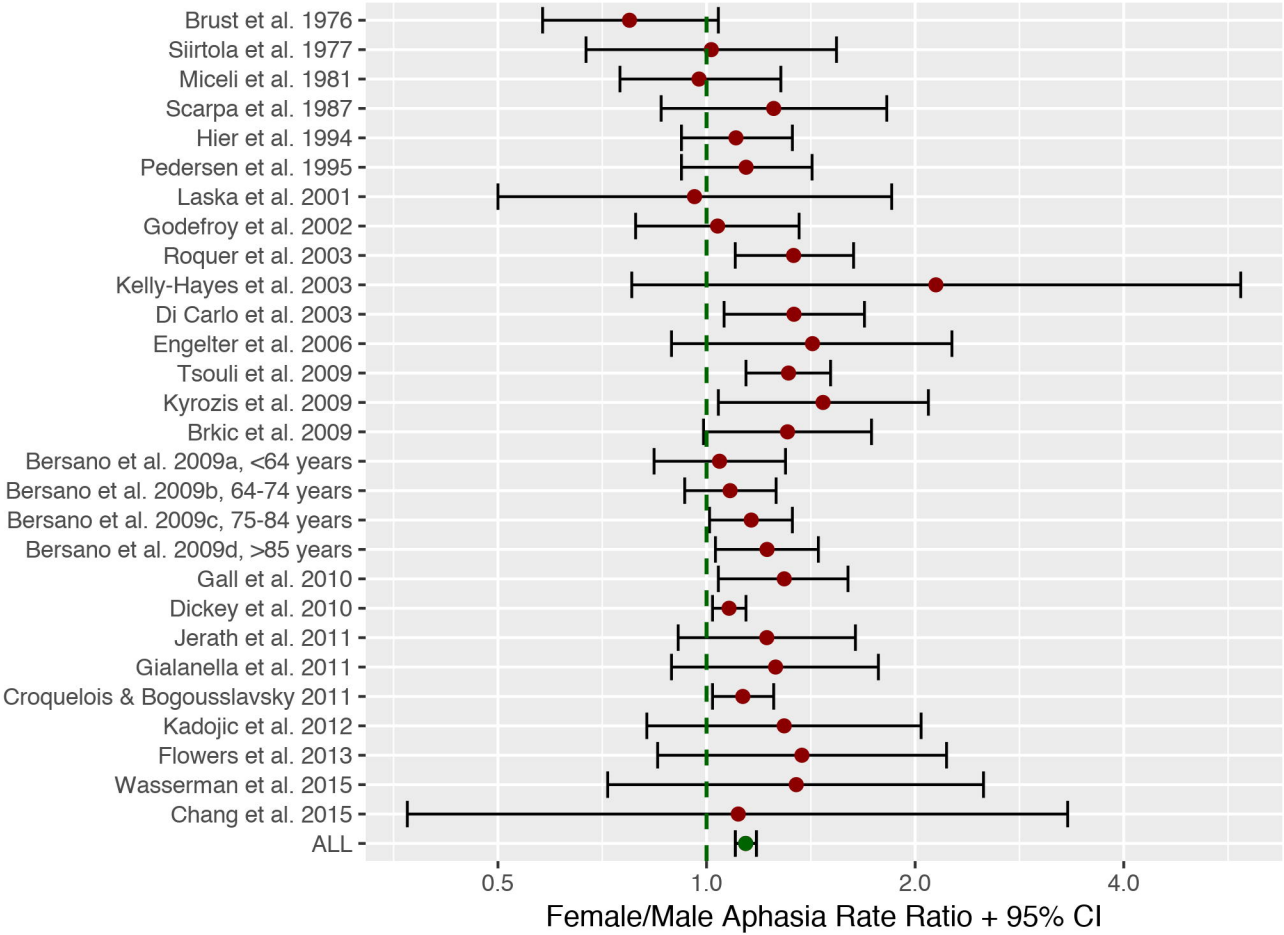
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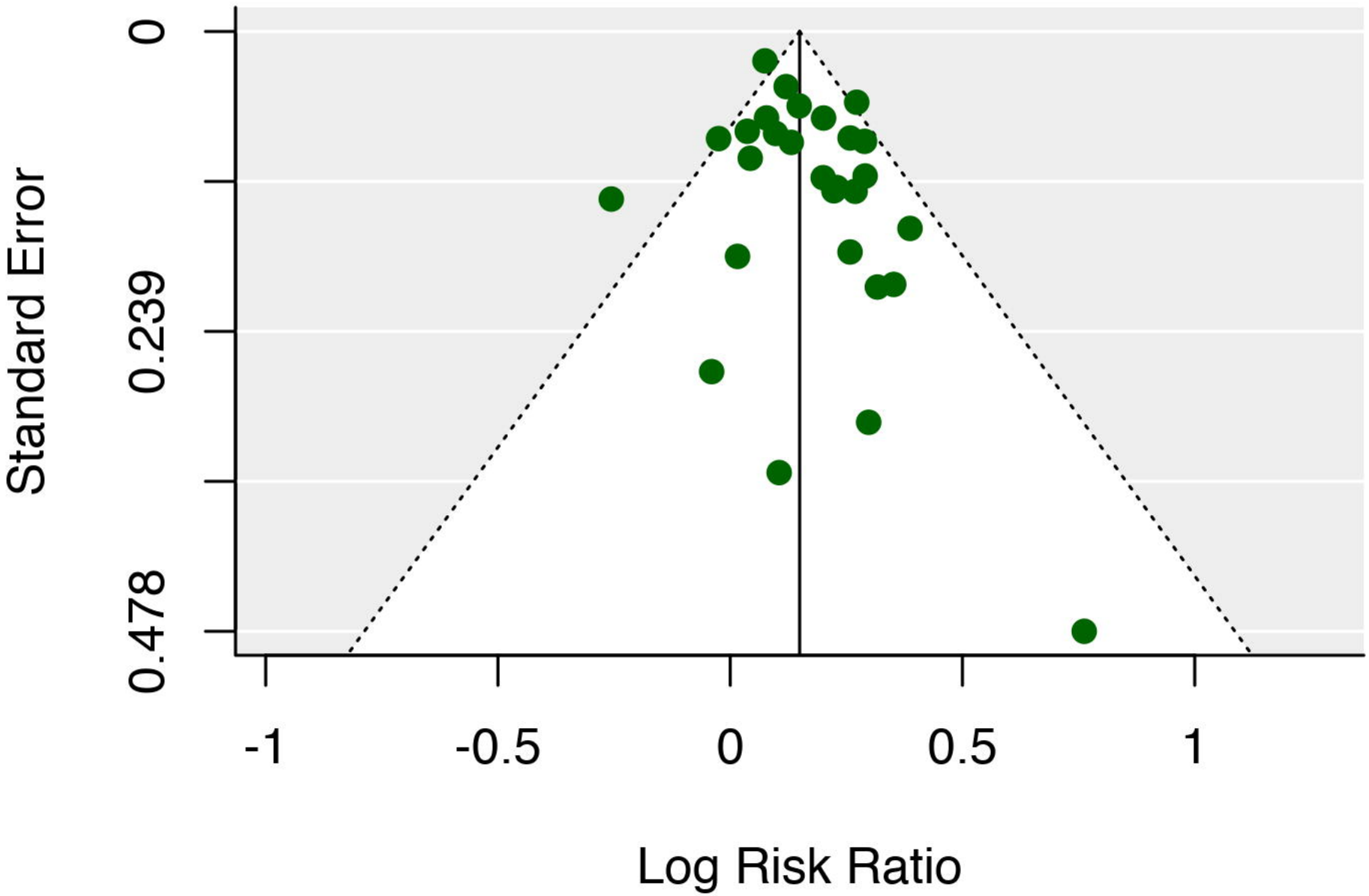
Female/Male Aphasia Rate Ratio + 95% CI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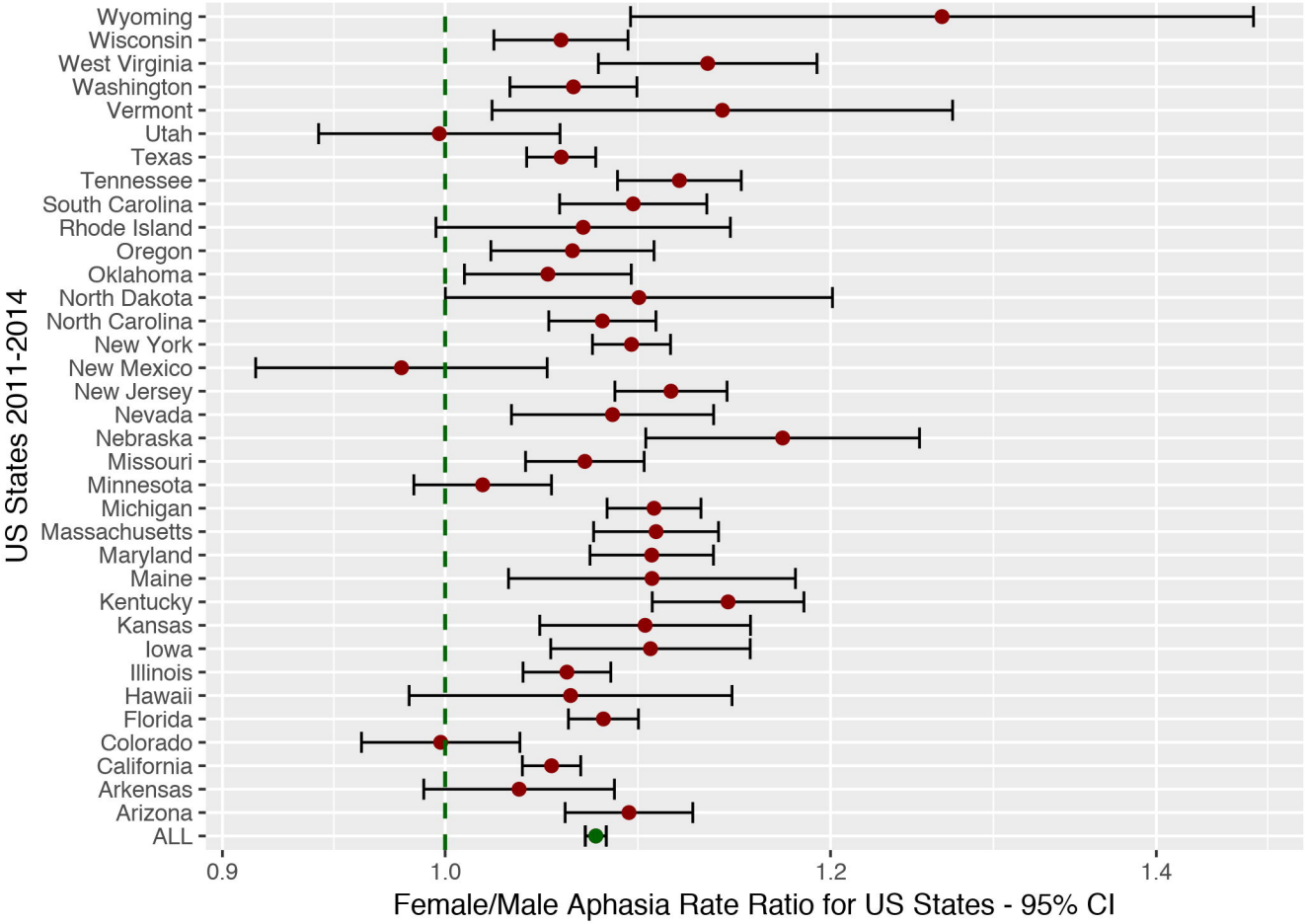
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US States 2011-2014
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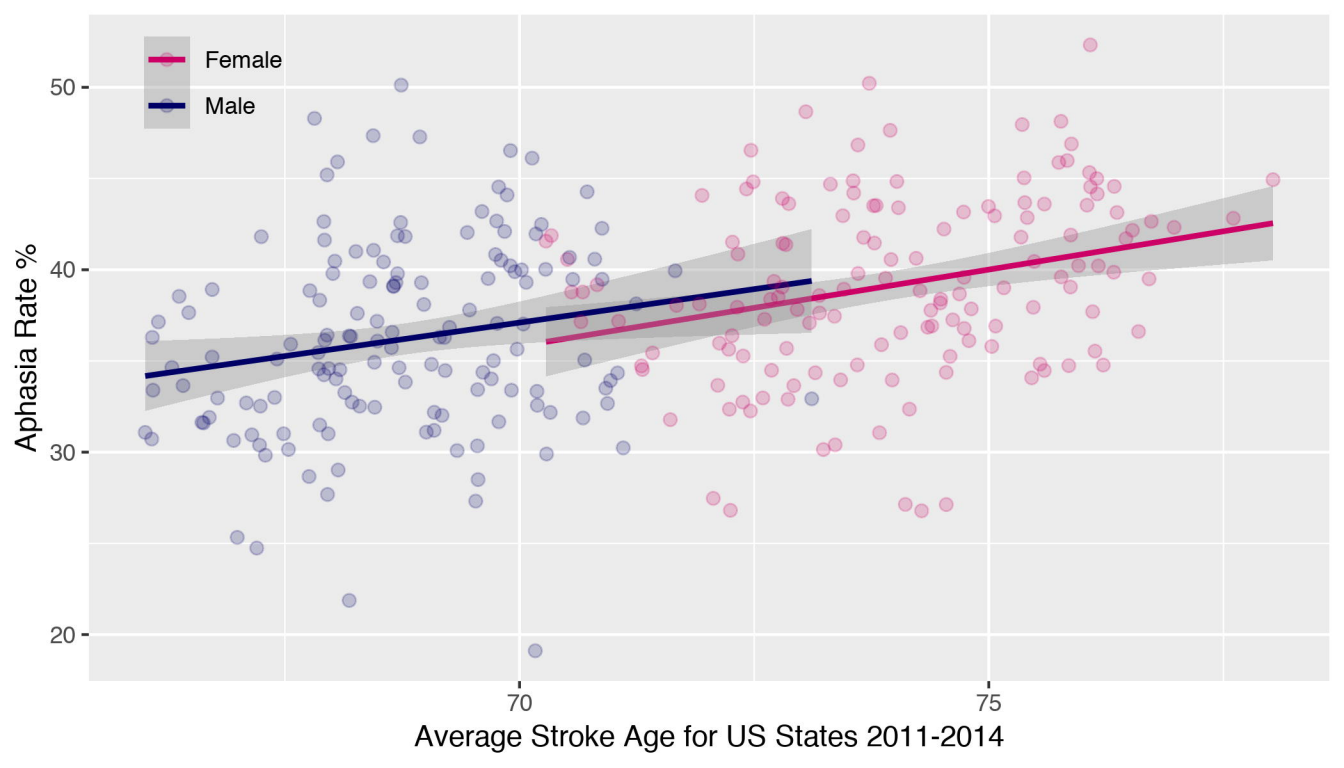
Female/Male Aphasia Rate Ratio for US States - 95% CI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Average Stroke Age for US States 2011-2014