










## ORIGINAL ARTICLE

# Impact of post-stroke aphasia on functional communication, quality of life, perception of health and depression: A case-control study

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## Abstract

**Background and purpose:** Post-stroke aphasia is associated with a reduced quality of life (QoL) and higher risk of depression. Few studies have addressed the effect of coping with aphasia. Our aim is to evaluate the impact of post-stroke aphasia on self-reported QoL and symptoms of depression.

**Methods:** This was a cross-sectional prospective case-control study. Cases involved patients with post-stroke aphasia included in the DULCINEA trial (NCT04289493). Healthy controls were recruited using snowball sampling. All subjects completed the following questionnaires: General Health Questionnaire (GHQ-12), Stroke Aphasia Quality of Life Scale (SAQOL-39), Communicative Activity Log (CAL) and Stroke Aphasic Depression Questionnaire (SADQ-10).

**Results:** Twenty-three patients (eight women; mean age 62.9 years) and 73 controls (42 women; mean age 53.7 years) were included. Cases scored lower than controls in perception of health (GHQ-12: median 3 [IQR 1; 6] vs. 0 [IQR 0; 2]) and perception of QoL (SAQOL-39: median 3.6 [IQR 3.3; 4.0] vs. 4.6 [IQR 4.2; 4.8]). Functional communication (CAL: median 135 [IQR 122; 148] vs. 94 [IQR 74; 103]) and SAQOL-39 communication subscale (median 2.7 [IQR 2.1; 3.2] vs. 4.8 [IQR 4.6; 5.0]) were also significantly lower in the case group. Notably, cases reported fewer depressive symptoms than controls (SADQ-10: median 11 [IQR 9; 15] vs. 13 [IQR 11; 16];  $p=0.016$ ). A mediational analysis revealed that the relationship between post-stroke aphasia and depression was not mediated by functional communication.

**Conclusions:** Although communication difficulties impact the QoL of patients with post-stroke aphasia, such patients report fewer depressive symptoms on the SADQ-10 scale than healthy people, with no differences in scores related to social participation.

## KEYWORDS

aphasia, communication, depression, quality of life, stroke

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## INTRODUCTION

Post-stroke aphasia is a common complication after ischaemic stroke, affecting approximately 15%–42% of stroke survivors. Aphasia is characterized by the impairment of all or some language modalities, including the production and understanding of speech, reading and writing. Post-stroke aphasia is associated with an increased mortality rate, long-term disability and decline in quality of life (QoL) [1]. Some studies suggest that one in four post-stroke patients eventually become depressed [2], with aphasia being identified as a major risk factor [3]. However, the actual prevalence and overall impact of depression amongst people with aphasia may be underreported in the literature due to the exclusion of patients with moderate to severe communication impairments from most studies [3]. The reported prevalence of post-stroke depression in systematic [3] and narrative reviews [4] is approximately 52%, which is higher than the 38% (95% confidence interval 33–43) cumulative pooled incidence of depression at 1 year after stroke in the overall stroke population [2].

As a vital aspect of daily functioning, communication is the most important predictor of social reintegration after a stroke [5]. In this regard, several studies and narrative systematic reviews have underscored the mediating role of functional communication in key outcomes of post-stroke aphasia, including reduced QoL and depression [6]. Therefore, the evaluation of functional communication is critical to assessing QoL in people with aphasia [7].

However, few studies have addressed the effect of living with post-stroke aphasia. Individuals with chronic illness progressively develop coping mechanisms to manage their disease and disability, and stroke survivors are no exception. In fact, several qualitative studies and systematic reviews have suggested that the perception of 'living successfully' is a dynamic, complex and highly individualized concept, composed of different aspects including leading an active lifestyle, having meaningful relationships and striving for positive ways to communicate with others [8, 9]. Moreover, QoL is often influenced by individual and contextual factors such as personality, social support and age, amongst others [10]. To fully evaluate the actual impact of post-stroke aphasia in QoL, mood and health, it is therefore necessary to compare the perceptions of people with aphasia with those of healthy controls.

The aim of this study was to assess the impact of post-stroke aphasia on functional communication, perceptions of QoL, health and mood compared to healthy controls. In addition, an exploration of the potential mediating role of residual functional communication on depressive symptoms and QoL in people with post-stroke aphasia was carried out.

## METHODS

To address these questions, a prospective cross-sectional case-control study was developed. The case group consisted of patients with post-stroke aphasia included in the DULCINEA trial

(NCT04289493). Full details of the design of this clinical trial are available elsewhere [11]. Briefly, the primary inclusion criteria were as follows: (i) non-fluent aphasia due to ischaemic stroke in the left hemisphere without neuroimaging evidence of lesions in the right hemisphere; (ii) standard programme of conventional speech therapy, previously completed; (iii) severely restricted language; poor repetition even for single words, and moderately preserved language comprehension (i.e., not exceeding the 70th percentile on the Repetition Scale plus exceeding the 15th percentile on the Listening Comprehension Scale, as an average score in word comprehension and command subscales and complex ideational material) in the Boston Diagnostic Aphasia Examination (BDAE) [12]; and (iv) signed informed consent. Exclusion criteria were (i) any clinical condition or other characteristic precluding appropriate follow-up; and (ii) simultaneous participation in any therapeutic trial assessing post-stroke recovery. Recruitment started in December 2020 and ended in February 2023.

The control group was composed of healthy individuals recruited using the non-probabilistic snowball procedure, successively sending an electronic questionnaire through different social media (WhatsApp, Twitter, Facebook). No formal sample calculation was performed. All the answers collected during the months of March and April 2022 were retrieved. Before responding to the electronic questionnaire, participants were informed of our adherence to local legal and ethical regulations regarding data protection and asked for their informed consent. Participant responses were anonymous and analysed collectively, thus ensuring the duty of confidentiality. Exclusion criteria were as follows: respondents (i) under 35 years of age, (ii) who had suffered a stroke, (iii) who were primary carers or relatives of a person with aphasia and (iv) with a language disorder (aphasia, dysarthria, dyslexia, mutism) or currently under treatment with antidepressants were excluded.

All subjects completed the General Health Questionnaire (GHQ-12) and the Stroke Aphasia Quality of Life Scale (SAQOL-39), as recommended by the Research Outcome Measurement in Aphasia (ROMA) Consensus statement [13–15]. The GHQ-12 is a screening instrument designed to evaluate psychological well-being, already validated for use in Spain [16]. It can be scored on a Likert scale, with a maximum score of 36, or with the GHQ, with a maximum score of 12; higher scores in both cases indicate poorer psychological well-being. For this study, the GHQ scoring method [16] was used. The SAQOL-39 is a useful tool to evaluate quality of life divided into four domains: physical, psychosocial, communication and energy. SAQOL-39 scores range from 1 to 5, with higher scores indicative of better QoL.

The Stroke Aphasic Depression Questionnaire (SADQ-10) [17] was used to detect a depressed mood (maximum score 30; higher scores indicate more severe symptoms of depression). A cut-off score of 14 points has been proposed to detect depression [18].

Finally, to measure functional communication the Communicative Activity Log (CAL) [19] was used. The CAL includes two measures (amount and quality of communication) with a maximum score of 90 each and higher scores reflect better performance.

For cases, these tests were recorded at the baseline visit of the DULCINEA trial to avoid the effect of the experimental therapy on the outcomes. All tests were administered by psychologists online due to the restrictions imposed by the COVID-19 pandemic. The CAL and SADQ-10 were completed by the patients' relatives, whilst the SAQOL-39 and GHQ-12 were completed by the patients themselves. To reduce any interference from the virtual platform in the completion of the tests by participants with severe expressive aphasia, all questions and potential answers were reinforced on the display and patients were allowed to point to the selected answer. Moreover, the support of a family member/accompanying person was allowed during the interview to facilitate the online connection and to ensure the proper understanding of the questions. For the controls, all tests were included in the online survey and were self-completed.

Data are shown as absolute and relative frequencies for categorical variables or median and interquartile range (IQR) for numeric variables. Data were first compared using a chi-squared test, Student's *t* test or Mann-Whitney's *U* test, as appropriate. To improve the adjustment of baseline differences between groups, ANOVA models were developed including age and sex as model covariates for the outcomes that were compliant with the ANOVA assumptions, using a Bonferroni-adjusted  $\alpha$  of 0.01667. Finally, Sobel tests [20, 21] were conducted for the mediation analysis of functional communication as mediating variable using depression and quality of life as potentially mediated variables. All analyses were conducted with IBM SPSS Statistics Version 28.0.1.0 (Chicago, IL, USA).

This study was approved by the local ethics committees and all participants (or their family members, if appropriate) signed the study informed consent. An aphasia-friendly information sheet in large text and simplified language was provided for participants with post-stroke aphasia.

## Patient and public involvement

The patient association Afasia Activa is a partner of the research consortium. Patients and their advisors were not involved in the design, recruitment or conduct of this study.

## Data sharing

The minimal anonymized dataset will be deposited in the official repository of the Madrid Health Government upon publication of the study results.

## RESULTS

Forty-four patients signed informed consent for the DULCINEA trial but 21 were excluded at the screening visit. The reasons for exclusion are detailed in Figure 1. The demographic and clinical data of the 23 patients with post-stroke aphasia included are detailed in Table 1. Eight (34%) were female with a mean age of 62.9 years. All the patients were in a chronic state of aphasia, with a median time from stroke onset of 24 months (IQR 13–77; range 6–237). Seven (39%) patients had aphasia lasting 5 years or more. The mean number of already completed speech and language therapies (SLTs) was 2 (SD 1.3). At the baseline evaluation, the median BDAE comprehension score was 26 (IQR 19–31) and the median BDAE repetition score was 5 (IQR 4–7). The primary family member/accompanying person assisting the patient in the completion of the tests was a spouse in nine cases (39%), son or daughter in six (26%), a sibling in one case (4.3%) and informal carer in another (4.3%). All but three (87%) had children and 12 (52%) grandchildren. Eight patients (34%) reported diagnoses of depression.

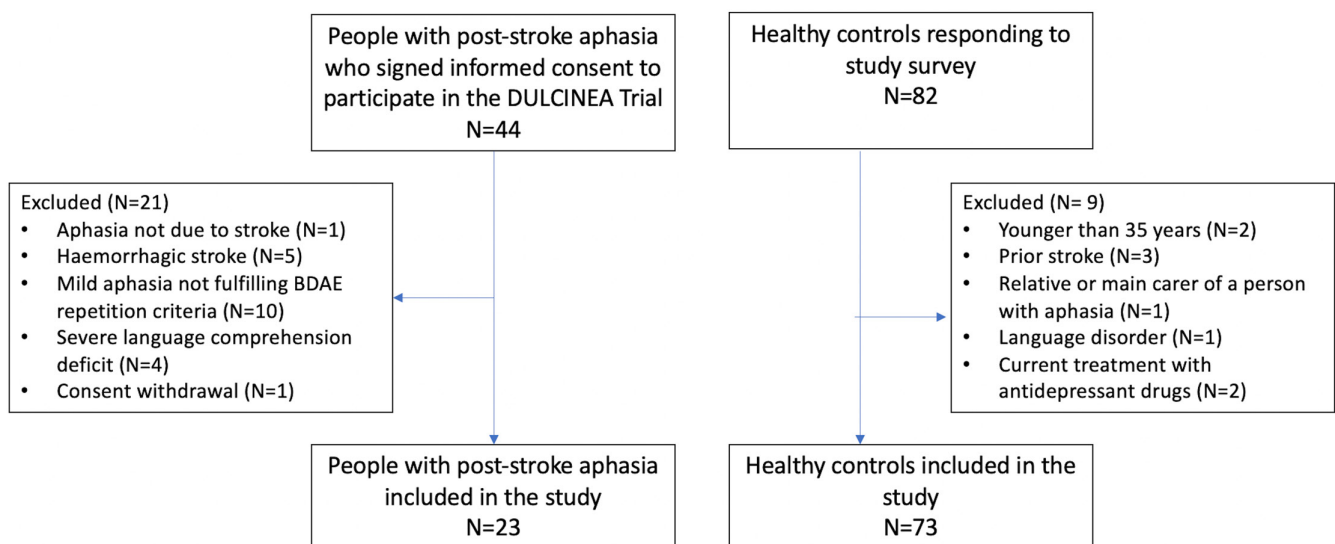


FIGURE 1 Study flowchart.

**TABLE 1** Demographic and clinical data of the case group.

	Cases (N=23)
Age, mean (SD)	62.9 (11.4)
Female, n (%)	8 (34)
Educational level	
Primary school	6 (26)
Secondary school	9 (39)
University	7 (30)
Right-handed	21 (91.3)
Primary language	
Spanish	23 (100)
Other languages learned	
Catalan	1 (4.3)
English	6 (26)
French	5 (21.7)
German	1 (4.3)
Italian	2 (8.7)
Marital status	
Married/has partner	12 (52)
Widowed	5 (21)
Single	5 (21)
Living circumstances	
Lives alone	4 (17)
Lives with relatives	19 (82)
Chronic diseases	
Hypertension	12 (52)
Diabetes	3 (13)
Cardiopathy	11 (47)
COPD	2 (8)
Hemiparesis	14 (60)
History of depression	8 (34)
Number of prior SLTs, median (IQR)	2 (1; 2)
Median time from stroke, months (IQR)	24 (13–77)

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SLT, speech and language therapy.

In terms of the control group, a total of 82 healthy individuals responded to the questionnaire. Nine were excluded under the exclusion criteria (two respondents were under 35 years of age, three reported having suffered from a stroke, one was the primary carer of a person with aphasia, one suffered from a language disorder and two reported they were under treatment with antidepressants). Ultimately, the responses from 73 healthy controls were analysed (Figure 1). A total of 42 (57.5%) were female and the mean age was 53.6 years, both parameters being significantly different from those of the cases.

Cases scored lower than controls in the perception of health measured by the GHQ-12 and in the perception of QoL (both in terms of the SAQOL-39 total score as well as in all the SAQOL-39

domains: physical, communication, psychosocial and vitality scales), the greatest difference being observed in communication (Table 2). Functional communication was also lower than controls in the CAL total score as well as in the measures of amount and quality of communication (Table 2). It is worth noting that respondents in the case group had significantly lower scores on the SADQ-10 scale, indicating fewer symptoms of depression (Figure 2). Specifically, they reported lower frequencies in the following behaviours: weeping spells, restless disturbed nights, bursting into tears, restlessness and keeping occupied during the day, with no differences in behaviours more closely related to social participation such as avoiding eye contact, refusing to participate in social activities or sitting without doing anything (Figure S1). There was a trend for the control group to have a higher frequency of scores  $\geq 14$  points than the case group (34 [46.6%] vs. 7 [30.4%];  $p = 0.130$ ).

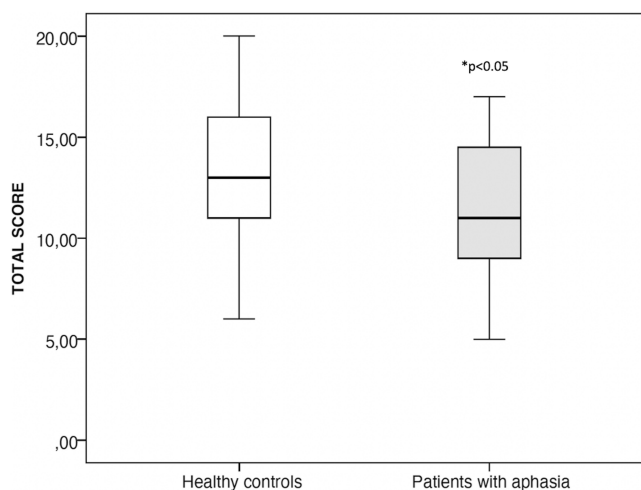
Outcome variables were further screened for standard ANOVA assumptions. The summary indices for QoL (SAQOL composite score), communication (CAL total score) and depression (SADQ-10) met normality and homogeneity assumptions and had three or fewer outliers, with the exception of the SAQOL composite score which did not meet the normality assumption for controls. Self-reported health (GHQ-12) and scale subdomains were not included in the final ANOVA because of not complying with standard assumptions and due to significant collinearity across scale subdomains. Age and sex were included as model covariates. The analyses revealed significant effects of post-stroke aphasia for QoL ( $F(3, 96) = 10.48$ ,  $p < 0.001$ ,  $\eta^2 = 0.26$ ), functional communication ( $F(3, 96) = 27.11$ ,  $p < 0.001$ ,  $\eta^2 = 0.47$ ) and depression ( $F(3, 96) = 6.90$ ,  $p < 0.001$ ,  $\eta^2 = 0.16$ ) (see Table 3 for details). As expected, the outcome on which post-stroke aphasia had the greatest impact was functional communication, accounting for 45% of the variance in total CAL scores, with both the quality and quantity subdomains contributing to this effect. Variations in QoL outcomes were also determined by post-stroke aphasia, albeit to a more modest extent, primarily driven by the communication subdomain. A post hoc analysis indicated that post-stroke aphasia explained 75% of the variance in the SAQOL communication scores,  $F(3, 96) = 85.41$ ,  $p < 0.001$ ,  $\eta^2 = 0.74$ . Finally, a counterintuitive low-magnitude effect of post-stroke aphasia on depression scores was found.

An ancillary mediational analysis revealed that the relationship between post-stroke aphasia and depression was not mediated by functional communication due to the near-zero regression coefficient between communication (predictor) and depression (outcome) (Figure 3). The lack of mediating effect may be attributable to the quadratic rather than linear distribution of the SADQ-10 scores amongst cases. An ancillary curvilinear regression analysis revealed an unstandardized  $\beta$  of 20.35 ( $p = 0.069$ ,  $R^2 = 0.40$ ) for the quadratic regression between communication (predictor) and depression (outcome), relative to a negligible 0.32 ( $p > 0.1$ ,  $R^2 = 0.05$ ) for linear regression (Figure 4). This apparent curvilinear association, which was specific to cases, showed a statistical trend that will need to be verified in future studies.

**TABLE 2** Comparison of median scores in the tests performed by cases and controls.

	Cases, N=23	Healthy controls, N=73	p
Psychological well-being			
GHQ-12 total score, median (IQR)	3 (1; 6)	0 (0; 2)	0.004
Quality of life			
SAQOL total score, median (IQR)	3.6 (3.3; 4.0)	4.6 (4.2; 4.8)	0.000
SAQOL physical scale, median (IQR)	4.0 (3.2; 4.5)	4.9 (4.7; 5.0)	0.000
SAQOL communication scale, median (IQR)	2.7 (2.1; 3.2)	4.8 (4.6; 5.0)	0.000
SAQOL psychosocial scale, median (IQR)	3.9 (2.9; 4.3)	4.3 (3.7; 4.9)	0.006
SAQOL vitality scale, median (IQR)	4.0 (3.2; 4.2)	4.5 (3.7; 4.7)	0.006
Functional communication			
CAL total score, median (IQR)	94 (74; 103)	135 (122; 148)	0.000
CAL amount of communication, median (IQR)	52 (45; 58)	65 (59; 71)	0.000
CAL quality of communication, median (IQR)	36 (29; 50)	71 (63; 77)	0.000
Depressed mood			
SADQ-10, median (IQR)	11 (9; 15)	13 (11; 16)	0.016

Abbreviations: CAL, Communicative Activity Log; GHQ-12, General Health Questionnaire; IQR, interquartile range; SADQ-10, Stroke Aphasic Depression Questionnaire; SAQOL-39, Stroke Aphasia Quality of Life Scale.



**FIGURE 2** SADQ-10 total score.

The mediation analysis of functional communication over the impact of case status on QoL (Figure 5) provided more significant results. The magnitude of the mediated effect was considerably higher than the direct effect ( $Z = -6.15 \pm 0.12$ ,  $p < 0.0001$ , vs.  $\beta = -0.84 \pm 0.15$ ,  $p < 0.001$ ). This analysis clearly suggests that communication ability exerts a strong mediating effect on the impact of post-stroke aphasia status on QoL.

## DISCUSSION

In this study it has been demonstrated that, although communication difficulties impact both the perception of health and QoL of people with post-stroke aphasia, these patients report fewer depressive

symptoms than healthy controls. This may be explained by the development of meaningful and context-specific strategies to adjust to and manage life after stroke, as has been suggested in previous qualitative studies and reviews [9, 10, 22]. Living successfully with aphasia has been related to topics such as participation, community integration, life roles, coping, adjustment and QoL [9]. With no difference in the scores of the items more closely related to social participation in the SADQ-10 scale compared to healthy controls, the results of our study reinforce the positive role of social participation in people with post-stroke aphasia.

Nevertheless, this does not seem to suffice to achieve equipoise in the perception of QoL. In this regard, some studies have reported poor perception of QoL in people with aphasia by means of the SAQOL-39 in both the acute and chronic phases after stroke, showing improvements over time [23–25]. In our study the domain with the lowest scores was that related to communication, with the mediational analysis confirming the strong effect of functional communication on QoL in patients with post-stroke aphasia. It was found that language impairment was that which most subjectively impacted QoL, despite involving a sample of stroke survivors with chronic aphasia and having completed standard SLT. However, as was also observed in our study, the relationship between post-stroke aphasia and depression does not seem to be significantly mediated by functional communication.

The primary contribution of our study is the comparison with healthy controls inasmuch as many studies evaluating mood and QoL in post-stroke aphasia patients compare them to stroke patients without aphasia. However, because the controls in these studies could be impacted by other neurological deficits, such comparisons may not provide an accurate representation of the consequences of post-stroke aphasia in daily life. Although, as

	Cases		Controls		ANOVA		
	M	SD	M	SD	F	$\eta^2$	R <sup>2</sup>
QoL, SAQOL							
Total	3.60	0.60	4.44	0.63	10.48***	0.26	0.23
Physical	3.87	0.91	4.74	0.43			
Communication	2.68	0.84	4.78	0.33			
Psychosocial	3.74	0.79	4.26	0.66			
Vitality	3.70	0.81	4.15	0.88			
Communication, CAL							
Total	90.35	25.65	134.73	18.86	27.11***	0.47	0.45
Amount	50.83	11.78	65.74	7.97			
Quality	39.52	15.27	71.29	9.81			
Depression, SADQ-10							
Total	11.30	3.57	13.53	3.46	6.90***	0.18	0.16

Note: *p* values are Bonferroni adjusted for multiple comparisons. Degrees of freedom 3. Age and gender included as covariables in all comparisons. Observed power above 0.9.

Abbreviations: CAL, Communicative Activity Log; QoL, quality of life; SADQ-10, Stroke Aphasic Depression Questionnaire; SAQOL-39, Stroke Aphasia Quality of Life Scale.

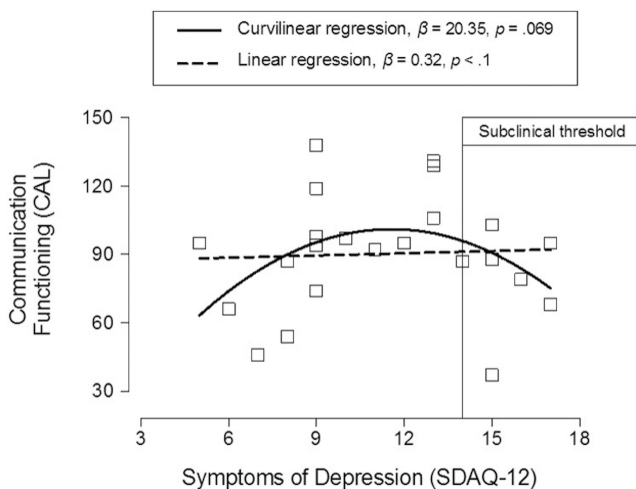
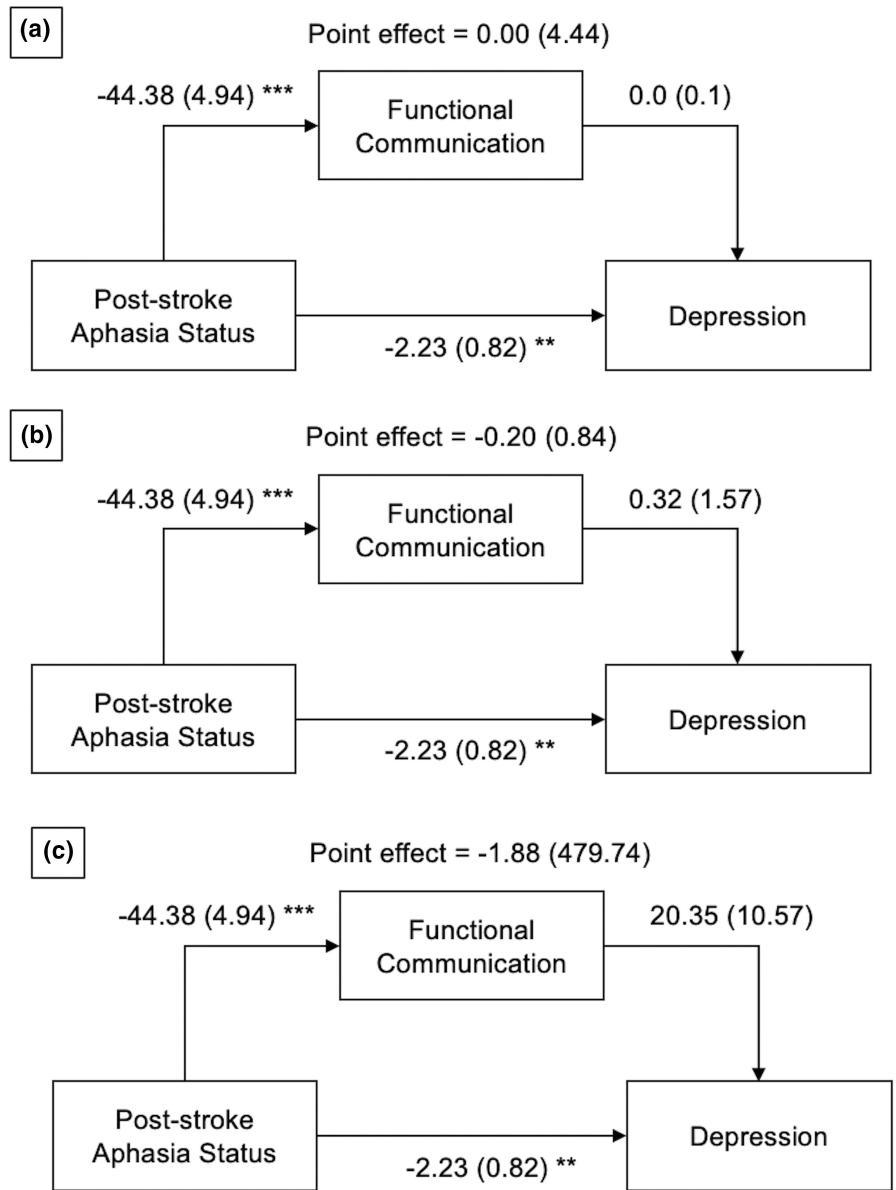
\*\*\**p* < 0.001.

**TABLE 3** Multivariate analysis of variance of quality of life (QoL), functional communication and depression amongst post-stroke aphasia cases (*n* = 23) and healthy controls (*n* = 73).

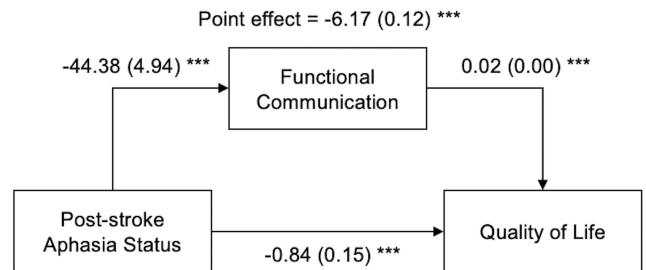
expected, the patients in our study scored lower in tests assessing communication, surprisingly they also reported fewer depressive symptoms than healthy controls. Beyond the potential long-term effect of coping with aphasia, an alternative explanation for the higher scores in the SADQ-10 scale in healthy controls could be the effect of the COVID-19 pandemic on the general population, as the study was conducted during the period immediately following. Along these lines, other authors have also observed lower rates of depression and anxiety in people with aphasia compared to elderly matched controls, which would seem to suggest that people with aphasia may have been to some extent spared the effect of the pandemic in the development of depressive symptoms, given that they already live in a state of social isolation and emotional instability, and these conditions might, paradoxically, have limited the effects of the coronavirus pandemic [26]. Although the authors also reported greater depressive symptoms in individuals with aphasia compared with pre-pandemic scores [26], it appears that the impact on healthy individuals has been higher, and our results might be interpreted as the reflection of the impact of COVID-19 on the emotional state of the general population. The data showing 46.6% of the controls with SADQ-10 scores  $\geq 14$  are in the range of the depression prevalence reported in the general population during the COVID-19 pandemic [27]. A potential limitation for the interpretation of differences in the presence of depressive symptoms is the fact that the SADQ-10 was developed for patients with aphasia and has not been validated for use in healthy individuals. Nevertheless, this scale explores behaviours that are also common in those without aphasia but with depression. Examples include weeping spells, restless disturbed nights, bursting into tears, restlessness, avoiding eye contact, refusing to participate in social activities and sitting without doing anything.

Our study has several limitations. First, the small sample size is a limitation although it is within the typical range of other studies reporting QoL in people with aphasia [22, 28]. Secondly, because all the people with aphasia in our study were already recruited in a clinical trial with restrictive inclusion and exclusion criteria, a selection bias cannot be ruled out. All were patients in a chronic phase (more than 6 months from stroke onset and having completed standard SLT) who were willing to take part in a clinical trial. This profile could represent a group of patients without depression, with a hope for further recovery and a more adaptive response to communication limitations than other patients who might not be interested in taking part in clinical trials on stroke. Maintaining a sense of hope and progression towards recovery has been reported to be an important contributor to managing successful life after stroke [10]. Nevertheless, up to 34% of the patients with post-stroke aphasia in our study had been diagnosed with depression, and 30.4% had scores  $\geq 14$  on the SADQ-10 at the evaluation. Moreover, the patients included were representative of people in a chronic phase after stroke with severely restricted language defined by poor repetition even for single words and moderately preserved language comprehension in the BDAE [12] despite the completion of standard SLTs [11]. In fact, the low values in the CAL test confirm the impaired functional communication of the patients included. Thirdly, healthy controls were recruited using a non-probabilistic snowball procedure, by sending an electronic questionnaire through different social media; therefore, they may not be representative of the general population. Fourthly, age and gender differences at baseline may have influenced the results in the tests administered. However, a review of the literature found no supporting evidence of a relationship between gender and language or QoL outcomes in post-stroke aphasia [28].

**FIGURE 3** Mediation analysis of functional communication using linear regression with depression for all participants (a), linear regression for cases (b) and quadratic regression for cases (c).



**FIGURE 4** Quadratic versus linear regression of functional communication and depression amongst post-stroke aphasia cases.



**FIGURE 5** Mediating effect of functional communication on the impact of post-stroke aphasia status on quality of life. All unstandardized beta linear regression coefficients followed by standard errors in parenthesis. Point effect Sobel test according to MacKinnon et al. [21]. \*\*\* $p < 0.001$ .

The main strengths of this study are its prospective design and the complete description of the baseline characteristics of the patients included with post-stroke aphasia, as well as the overall

assessment of perception of health, QoL, mood and functional communication, using standard and validated tests, in accordance with current recommendations for post-stroke aphasia research, such as the DESCRIBE project [29] and the ROMA Consensus [13].

In conclusion, although communication difficulties affect the perception of health as well as the QoL of patients with post-stroke aphasia, these patients report fewer depressive symptoms than healthy people, with no differences in the scores most closely related to social participation. This reinforces the positive role of social participation in people with post-stroke aphasia.

#### AUTHOR CONTRIBUTIONS

Nereida Bueno-Guerra: Conceptualization; methodology; investigation; supervision; funding acquisition; resources. Marta Provencio: Data curation. Aida Tarifa-Rodríguez: Formal analysis; data curation; writing—review and editing; investigation. Ana Navarro: Data curation. Cristian Sempere-Iborra: Data curation. Pablo Jordi: Data curation. Elena de Celis-Ruiz: Investigation. María Alonso de Leciñana: Investigation. Marta Martín Alonso: Investigation. Ricardo Rigual: Investigation. Gerardo Ruiz-Ares: Investigation. Jorge Rodríguez-Pardo: Investigation. Javier Virués-Ortega: Formal analysis; data curation; writing—review and editing. Blanca Fuentes: Conceptualization; methodology; funding acquisition; resources; project administration; supervision; writing—review and editing; formal analysis; writing—original draft.

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#### CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interests related to this paper.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Repositorio Institucional de la Consejería de Sanidad at <https://repositoriosaludmadrid.es>.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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