

Sex differences in quality of life in stroke survivors: data from the 'Tinzaparin in Acute Ischaemic Stroke Trial' (TAIST)

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CONFLICTS OF INTEREST

Philip MW Bath was the Principal Investigator for the TAIST Trial. Gudrun Boysen, Peter Paul De Deyn, Didier Leys, Desmond O'Neill, E Bernd Ringelstein were members of the TAIST Advisory Committee. Philip Bath received honoraria from Leo Pharma A/S. Laura Gray, Nikola Sprigg, Gudrun Boysen, Peter Paul De Deyn, Didier Leys, Desmond O'Neill, and E Bernd Ringelstein have no conflicts of interest.

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Keywords: Acute stroke; ischaemic stroke; quality of life; functional outcome; sex

Word Count: 3335

ABSTRACT

Introduction: Female sex is predictive of poor functional outcome in stroke, even after correction for prognostic factors. Poor quality of life (QoL) is observed in stroke survivors, with lower scores seen in the most disabled patients. We used data from the TAIST trial to assess the relationship between sex and QoL after ischaemic stroke.

Methods: TAIST was a randomised controlled trial assessing the safety and efficacy of tinzaparin versus aspirin in 1,484 patients with acute ischaemic stroke. QoL was measured at 180 days post randomisation using the short-form 36 health survey which assesses QoL across eight domains. The relationship between sex and each domain was assessed using ordinal regression, both unadjusted and adjusted for key prognostics factors.

Results: Of the 1,484 patients randomised into TAIST, 216 had died at 180 days post randomisation. 1,268 survivors were included in this analysis, 694 males (55%), 574 females (45%). Females tended to score lower than males across all QoL domains (apart from general health); statistically significant lower scores were seen for physical functioning (odds ratio (OR) 0.58, 95% confidence interval (CI) 0.47-0.72), vitality (OR 0.79, 95% CI 0.64-0.98) and mental health (OR 0.75, 95% CI 0.61-0.93). The results for physical functioning and mental health remained significant after adjustment for prognostic variables (OR 0.73, 95% CI 0.58-0.92; OR 0.76, 95% CI 0.60-0.95 respectively).

Conclusions: QoL, in particular physical function and mental health domains, is lower in female patients after stroke. This difference persists even after correction for known prognostic factors such as age and stroke severity.

INTRODUCTION

Quality of life (QoL) is widely recognised to be impaired after stroke^{1, 2} and is related to post-stroke disability and handicap.³ It is clear that both motor and non-motor symptoms play an important role in recovery after stroke.⁴ As such, there is an increasing call for trials to monitor QoL in addition to other measures such as modified Rankin scale and Barthel Index in order to give a broader assessment of outcome after stroke.³

Outcome in female stroke patients has been reported to be worse than in males, with an increased risk of dependency and institutionalisation.⁵⁻⁷ However, female stroke patients tend to be older and more frail, which accounts for some of the worse prognosis. The relationship between QoL and sex is unclear; whilst some studies have observed lower QoL scores in females,⁸⁻¹¹ others have detected no sex difference.^{7, 12-}

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We sought to further assess the relationship between sex and QoL using data from the 'Tinzaparin in Acute Ischaemic Stroke Trial' (TAIST).¹⁵

METHODS

Subjects

TAIST compared the safety and efficacy of tinzaparin (low molecular weight heparin) given at high dose (175 anti-Xa IU/kg/day), tinzaparin at medium dose (100 anti-Xa IU/kg/day), and aspirin (300 mg od) in patients with acute ischaemic stroke.¹⁵

Subjects were included within 48 hours of stroke onset. All data were collected prospectively as part of the trial protocol.¹⁵

Quality of life

QoL was measured at 180 days after randomisation by a face to face interview¹⁵ using the short form 36 health survey,¹⁶ which assesses quality of life across eight domains: physical functioning; physical role; bodily pain; general health; vitality; social functioning; emotional role; and mental health.¹⁶ We used the transposed versions for each domain, so each are scored from zero to 100 with zero relating to the worst state of QoL and 100 relating to the best state.¹⁶ Summary scores were also calculated for the four physical and four mental domains.¹⁷ All patients completed the assessment themselves and proxies were not used.

Outcome

Outcome was measured using the modified Rankin Scale and Barthel Index at 180 days post randomisation.¹⁵

Statistical methods

Prognostic baseline factors were compared by sex using Fisher's exact test for categorical data and the Wilcoxon test for ordinal or continuous data. The relationships between sex, QoL domains, functional outcome, and discharge

disposition were assessed using ordinal regression or logistic regression, both unadjusted and adjusted for 8 key prognostic factors: age, baseline systolic blood pressure, severity (Scandinavian Stroke Scale), pre morbid modified Rankin Scale, pre morbid residency, history of myocardial infarction, stroke type (cardioembolic, large artery), and treatment group. To compensate for the imbalance in age between the sexes two matched analyses were also performed: (i) individual males and females were paired for age (within 3 years) and severity (within 3 points); and (ii) on age and severity (as in i), previous MI and type of stroke (cardioembolic, large artery). All analyses were performed using SAS (SAS Institute, Cary, North Carolina, USA). Where missing data occurred patients were excluded. Significance was taken at $p < 0.05$ and 95% confidence intervals are given.

RESULTS

Subjects

Of the 1,484 patients randomised into TAIST, 216 had died at 180 days post randomisation: 113 males (14%) and 103 females (15%). Hence, 1,268 survivors were included in this analysis: 694 males (55%), 574 females (45%). The baseline characteristics of included patients by sex are shown in table 1. Many prognostic factors were similar by sex, although females were older, more likely to have atrial fibrillation, a stroke of cardioembolic types, have lower pre morbid functional status (modified Rankin Scale (mRS)), more likely to be in a nursing home, and were less likely to have suffered a previous myocardial infarctions or had a stroke of large artery type.

Quality of Life

Females had lower QoL scores than men, in particular relating to physical functioning, vitality, and mental health (table 2). When adjusted for key prognostic factors (age, baseline systolic blood pressure, Scandinavian Stroke Scale, history of myocardial infarction, stroke type, pre morbid mRS, residency and treatment group) the differences in physical functioning and mental health remained statistically significant, with females reporting scores that were around 25% lower than males (table 2). Physical and mental summary QoL scores did not differ by sex after adjustment.

Outcome

The modified Rankin scale differed significantly by sex with females having a worse functional outcome at 6 months (unadjusted $p=0.001$; adjusted $p=0.26$ (table 2, figure 1). Similarly, Barthel Index scores were lower in females (unadjusted $p<0.0001$, adjusted $p=0.13$) (table 2). A poor functional outcome (mRS) was

associated with lower physical ($r_s=-6.3$, $p<0.0001$) and mental ($r_s=-0.2$, $p<0.0001$) QoL domains. Mortality was similar between males and females (table 2). At 6 months post randomisation, more males than females were resident in their own home; conversely, more females than males were resident in a nursing home (table 2, figure 2).

Matching of data by sex

Repeating the analysis on matched sub-sets of the TAIST data gave comparable results to the unmatched analysis (figure 3). The age and severity matched data and the age, severity, MI and stroke type matched data both showed that females had consistently worse QoL than males for all domains with statistically significant differences for physical functioning and mental health in both data sets, and additionally vitality and social functioning in the age and severity matched data.

DISCUSSION

The main finding in this study of patients with acute ischaemic stroke is that female patients have lower quality of life scores at 6 months than males, especially in the domains of physical function and mental health, and possibly vitality. Similar findings have been seen in earlier studies of QoL post stroke⁸⁻¹¹ as well as female patients with ischaemic heart disease.¹⁸ Earlier studies in stroke limited statistical adjustment to age¹¹ whereas we were able to correct for additional prognostic factors including severity and co morbidity. Furthermore, previous studies have assigned a score of zero to deceased patients,¹ which may exaggerate lower scores in females since they have a trend to increased mortality (as seen here). However, our findings were not confounded in this manner as dead patients were excluded from this analysis.

Despite demonstrating a relationship between sex and individual domain scores, we did not show any major relationship between summary scores and sex when adjusting for other prognostic factors. This is in keeping with previous work,^{19, 20} and is not surprising as the summation of domains can lead to the loss of data. At present there is little evidence to support the use of such summary scores.²⁰

Females also had a worse functional outcome, whether judged using the modified Rankin Scale or Barthel Index. These scales largely measure physical disability and dependency so it is unsurprising that the functional and physical QoL domains are interrelated and differ similarly by sex.

One possible explanation for the gender difference may arise from a difference in coping and adaptation patterns. In other illnesses, marked gender differences can be discerned,²¹ and the role of coping and adaptive strategies in stroke is a newly

developed field of interest.²² Females have also been shown to report lower QoL in a general population.²³ Another explanation for this difference may be the place of residence 6 months post stroke, with many more females being resident in a nursing home than males; QoL is likely to be less well rated in an institution than at home.

This study has several limitations. First, the data come from a randomised controlled trial which excluded both very mild and very severe strokes. Excluding mild strokes will tend to cause a floor effect in QoL domains, well recognised when using the SF-36.²⁰ (Excluding patients with very severe strokes is less of a problem since many die and therefore would not contribute QoL data.) Second, QoL was assessed at only one time point (6 months post stroke) despite temporal trends being recognised in both physical and mental domains of QoL.^{1,2, 10} Third, depression and QoL are associated with each other with depressed patients have a lower QoL. Although female stroke patients have an increased prevalence of post stroke depression,⁸ we could not take account of this since TAIST did not collect the relevant information. Finally, although the SF-36 is one of the most widely used measures of quality of life, it may not meet the specific demands of measuring quality of life after stroke as well as other measures²⁴ and may not accord sufficient priority to the subjective priorities of stroke patients in what is important in their quality of life.²⁵ Despite these limitations, these data come from a large high fidelity trial, and exhibit external validity.⁸⁻¹¹

In summary, female stroke patients have a lower quality of life, especially in the domains of physical and mental health, which is independent of age, stroke severity and aetiological type, and other co-morbid factors. Females also have a worse functional outcome. Since medicinal interventions such as aspirin and alteplase administration improve functional outcome, it will be important to determine if quality of life can also be modified therapeutically post stroke.

REFERENCES

1. Sturm JW, Donnan GA, Dewey HM, Macdonell RAL, Gilligan AK, Srikanth V, Thrift AG. Quality of life after stroke. The north east Melbourne stroke incidence study (NEMESIS). *Stroke*. 2004;35:2340-2345
2. Paul SL, Strum JW, Dewey HM, Donnan GA, Macdonell RAL, Thrift AG. Long term outcome in the north east Melbourne stroke incidence study. Predictors of quality of life at 5 years after stroke. *Stroke*. 2005;36:2082-2086
3. Patel MD, Tilling K, Lawrence E, Rudd AG, Wolfe CDA, McKeivitt C. Relationships between long-term stroke disability, handicap and health-related quality of life. *Age and Ageing*. 2006;35:273-279
4. Haacke C, Althaus A, Spottke A, Siebert U, Back T, Dodel R. Long-term outcome after stroke: Evaluating health-related quality of life using utility measurements. *Stroke*. 2006;37:193-198
5. Glader E-L, Stegmayr B, Norrving B, Terent A, Hulter-Asberg K, Wester P-O, Asplund K, For the Riks-Stroke Collaboration. Sex differences in the management and outcome after stroke. A Swedish national perspective. *Stroke*. 2003;34:1970-1975
6. Di Carlo A, Lamassa M, Baldereschi M, Pracucci G, Basile AM, Wolfe CD, M. G, Rudd A, Ghetti A, Inzitari D, European BIOMED Study of Stroke Care Group. Sex differences in the clinical presentation, resource use, and 3-month outcome of acute stroke in europe. Data from a multicenter multinational hospital-based registry. *Stroke*. 2003;34:1114-1119
7. Kapral MK, Fang J, Hill MD, Silver F, Richards J, Jaigobin C, Cheung AM, For the Investigators of the registry of the Canadian Stroke Network. Sex differences in stroke care and outcomes: Results from the registry of the Canadian stroke network. *Stroke*. 2005;36:809-814

8. Carod-Artal J, Egido JA, Gonzalez JL, de Seijas V. Quality of life among stroke survivors evaluated 1 year after stroke. Experience of a stroke unit. *Stroke*. 2000;31:2995-3000
9. Hackett ML, Duncan JR, Anderson CS, Broad JB, Bonita R. Health-related quality of life among long-term survivors of stroke. Results from the Auckland stroke study, 1991-1992. *Stroke*. 2000;31:440-447
10. Hopman WM, Verner J. Quality of life during and after inpatient stroke rehabilitation. *Stroke*. 2003;34:801-805
11. Nichols-Larsen DS, Clark PC, Zeringue A, Greenspan A, Blanton S. Factors influencing stroke survivors quality of life during subacute stroke recovery. *Stroke*. 2005;36:1480-1484
12. Moon Y-S, Kim S-J, Kim H-C, Won M-H, Kim D-H. Correlates of quality of life after stroke. *Journal of the Neurological Sciences*. 2004;224:37-41
13. Lai S-M, Duncan PW, Dew P, Keighley J. Sex differences in stroke recovery. *Preventing Chronic Diseases*. 2005;2:1-11
14. Ones K, Yilmaz E, Cetinkaya B, Caglar N. Quality of life for patients poststroke and factors affecting it. *Journal of Stroke and Cerebrovascular Diseases*. 2005;14:261-266
15. Bath P, Lindenstrom E, Boysen G, De Deyn P, Friis P, Leys D, Marttila R, Olsson J-E, O'Neill D, Orgogozo J-M, Ringelstein B, van der Sande J-J, Turpie AGG. Tinzaparin in acute ischaemic stroke (TAIST): A randomised aspirin-controlled trial. *Lancet*. 2001;358:702-710
16. Ware JE, Snow KK, Kosinski M, Gandek B. *Sf-36 health survey manual and interpretation guide*. Boston: MA:New England Medical Centre, The Health Institute; 1993.
17. Ware JE, Kosinski M, Keller SK. *Sf-36 physical and mental health summary scales: A user's manual*. Boston: MA: The Health Institute; 1994.

18. Riedinger MS, Dracup KA, Brecht M-L, Padilla G, Sarna L, For the SOLVD Investigators, Ganz PA. Quality of life in patients with heart failure: Do gender differences exist? *Heart and Lung*. 2001;30:105-113
19. Hobart JC, Williams LS, Moran K, Thompson AJ. Quality of life measurement after stroke: Uses and abuses of the sf-36. *Stroke*. 2002;33:1348-1356
20. de Haan RJ. Measuring quality of life after stroke using the sf-36. *Stroke*. 2002;33:1176
21. Christensen U, Schmidt L, Hougaard CO, Kriegbaum M, Holstein BE. Socioeconomic position and variations in coping strategies in musculoskeletal pain: A cross-sectional study of 1,287 40 and 50 year old men and women. *Journal of Rehabilitation Medicine*. 2006;38:316-321
22. Donnellan C, Hevey D, Hickey A, O'Neill D. Defining and quantifying coping strategies after stroke: A review. *Journal of Neurology, Neurosurgery and Psychiatry*. 2006;77:1208-1218
23. Guite HF, Clark C, Ackrill G. The impact of the physical and urban environment on mental well-being. *Public Health*. 2006;120:1117-1126
24. Buck D, Jacoby A, Massey A, Ford G. Evaluation of measures used to assess quality of life after stroke. *Stroke*. 2000;31:2004-2010
25. Hickey A, Barker M, McGee H, O'Boyle C. Measuring health-related quality of life in older patient populations: A review of current approaches. *Pharmacoeconomics*. 2005;23:971-993

TABLE 1. Baseline characteristics by sex.

Frequency (%), mean (standard deviation), or median [inter-quartile range]; comparison by Fisher's exact test, Chi-square test, or Mann Whitney U test.

	Total	Males	Females	P value
Subjects (%)	1268	694 (54.7)	574 (45.3)	-
Age (years)	70.7 (11.1)	68.4 (10.8)	73.4 (10.7)	<0.0001
Scandinavian Stroke Scale (/58)	36 [17]	36 [18]	35 [16]	0.12
Pre morbid Modified Rankin Scale	0 [1]	0 [0]	0 [1]	<0.0001
Pre morbid living at home	1212 (95.6)	674 (97.1)	538 (93.7)	0.004
Pre morbid nursing home	5 (0.4)	0 (0)	5 (0.9)	0.02
Systolic blood pressure (mmHg)	156 (22)	156 (22)	157 (23)	0.50
Previous stroke (%)	148 (11.8)	81 (11.8)	67 (11.9)	0.99
Previous transient ischaemic attack (%)	213 (17.4)	120 (17.9)	93 (16.8)	0.64
Atrial fibrillation (%)	126 (18.2)	57 (15.4)	69 (21.3)	0.05
Diabetes mellitus (%)	200 (15.9)	117 (17.1)	83 (14.5)	0.25
Previous myocardial infarction (%)	159 (15.2)	120 (17.6)	69 (12.2)	0.01

TOAST classification:

Cardioembolic	276 (21.9)	132 (19.1)	144 (25.3)	0.01
Large artery	412 (32.8)	263 (38.2)	149 (26.2)	<0.0001
Lacunar	502 (39.8)	268 (38.8)	234 (41.0)	0.45
Treatment assignment:				
Aspirin (%)	418 (33.0)	223 (32.1)	195 (34.0)	0.51
Medium dose tinzaparin (%)	435 (34.3)	246 (35.4)	189 (32.9)	0.37
High dose tinzaparin (%)	415 (32.7)	225 (32.4)	190 (33.1)	0.81

TABLE 2. Quality of life domains and summary scores, functional outcome and discharge disposition, by sex.

Median (inter-quartile range); comparison by ordinal regression or logistic regression, unadjusted and adjusted † (odds ratio, 95% confidence intervals).

	Male	Female	Unadjusted	Adjusted
Number (%)	694 (55)	574 (45)		
Physical functioning	50 [20-80]	35 [10-60]	0.58 (0.47-0.72)	0.73 (0.58-0.92)
Role-physical	25 [0-75]	0 [0-75]	0.90 (0.72-1.13)	0.92 (0.72-1.17)
Bodily pain	72 [51-100]	72 [51-100]	0.93 (0.75-1.15)	0.92 (0.73-1.16)
General health	62 [42-77]	60 [45-77]	1.25 (0.68-2.29)	1.32 (0.70-2.51)
Vitality	50 [35-70]	50 [35-65]	0.79 (0.64-0.98)	0.86 (0.69-1.08)
Social functioning	75 [50-100]	62.5 [37.5-100]	0.83 (0.67-1.03)	0.87 (0.69-1.10)
Role-emotional	66.7 [0-100]	66.7 [0-100]	0.94 (0.75-1.18)	0.93 (0.73-1.19)
Mental health	72 [56-88]	68 [52-84]	0.75 (0.61-0.93)	0.76 (0.60-0.95)
Physical summary	37.2 [30.0-45.9]	35.5 [28.6-43.8]	0.78 (0.62-0.97)	0.88 (0.70-1.10)
Mental summary	49.1 [38.7-57.7]	48.1 [38.1-58.3]	0.91 (0.73-1.13)	0.87 (0.69-1.10)
Modified Rankin Scale	2 [1-3]	3 [1-4]	1.41 (1.15-1.72)	1.13 (0.91-1.41)
Barthel Index	95 [75-100]	90 [65-100]	0.66 (0.54-0.81)	0.84 (0.67-1.05)

Living at home (%)	545 (82)	369 (67)	0.45 (0.34-0.58)	0.56 (0.41-0.77)
Nursing home (%)	68 (10)	102 (18)	1.99 (1.43-2.77)	1.36 (0.93-1.99)

‡ Adjustment for age, baseline systolic blood pressure, baseline severity, pre morbid mRS, pre morbid residency, history of MI, stroke type (cardioembolic, large artery), treatment group

FIGURE LEGENDS

FIGURE 1

Functional outcome (modified Rankin Scale) at 180 days by sex. Death was excluded as for analysis of quality of life.

FIGURE 2

Discharge disposition (residency) at 180 days by sex. Death was excluded as for analysis of quality of life.

FIGURE 3

Comparison of quality of life by sex: unmatched and matched analyses.

Plot shows odds ratio and 95% confidence intervals from ordinal regression analysis. All models adjusted for age, baseline systolic blood pressure, baseline severity, pre morbid mRS, pre morbid residency, history of MI, stroke type (cardioembolic, large artery), treatment group. PF: Physical functioning, RP: Role physical, BP: Bodily pain, GH: General health, V: Vitality, SF: Social functioning, RE: Role emotional, MH: Mental health.

FIGURE 1. Functional outcome (modified Rankin Scale) at 180 days by sex.

Death was excluded as for analysis of quality of life.

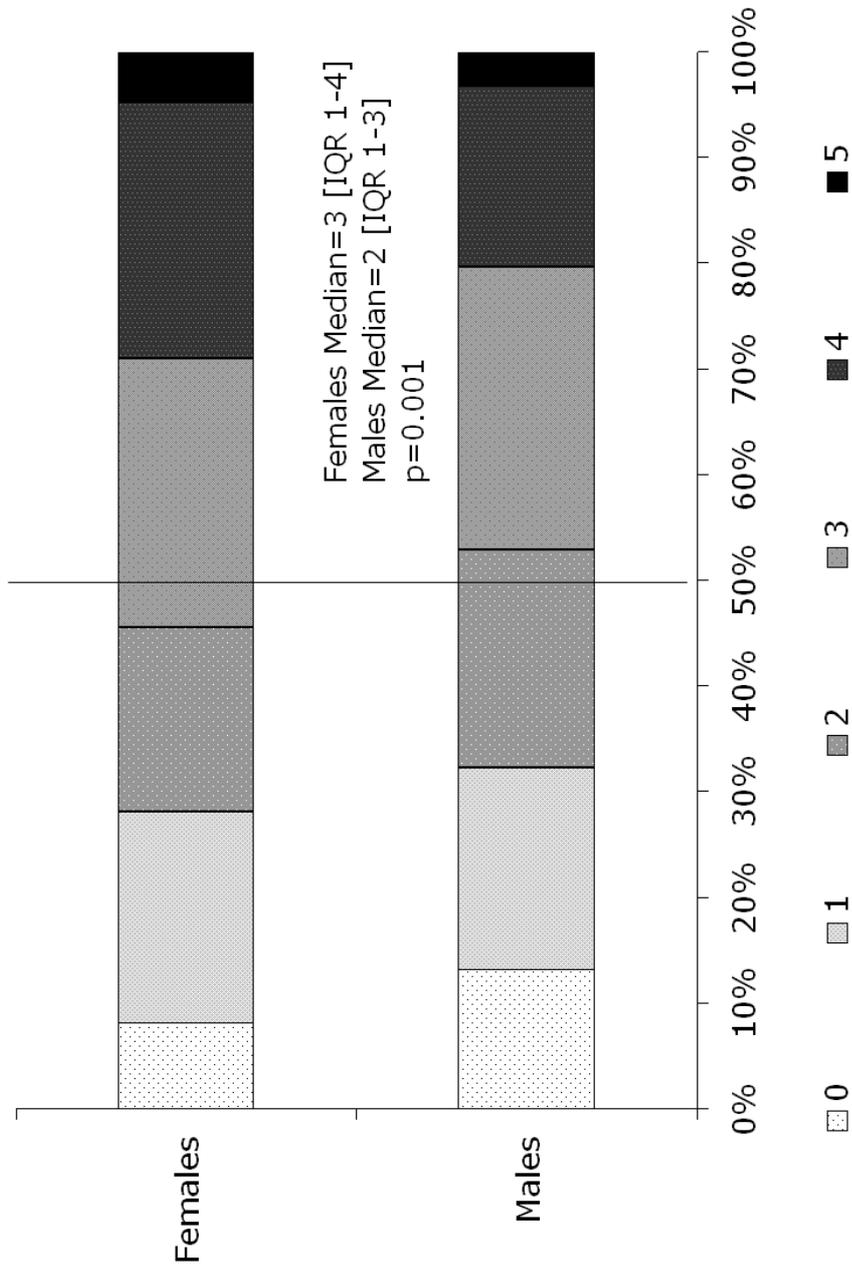


FIGURE 2. Discharge disposition (residency) at 180 days by sex.

Death was excluded as for analysis of quality of life.

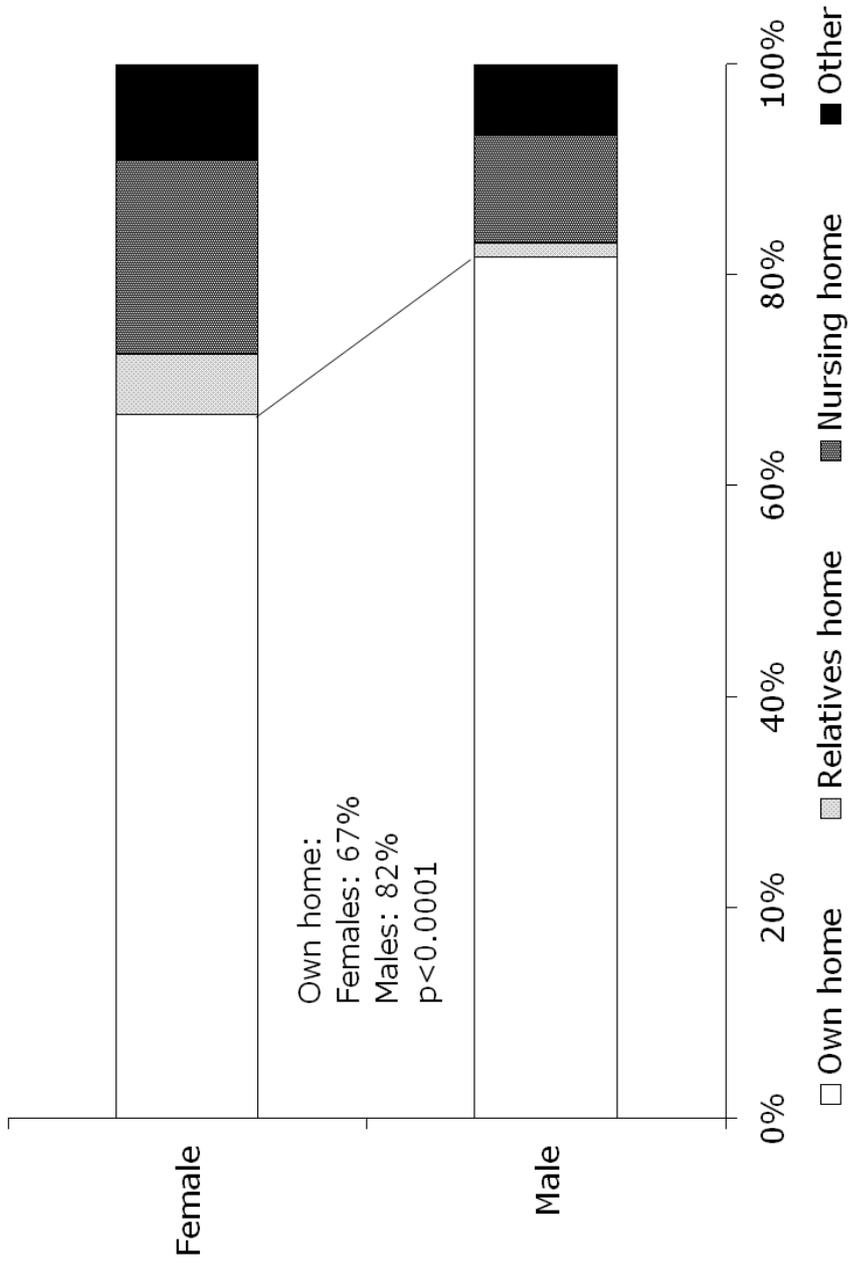


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