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Original Article

Comparison of Fallers and Nonfallers on Four Physical Performance Tests: A Prospective Cohort Study of Community-Dwelling Older Indigenous Taiwanese Women

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ABSTRACT

Background: In this study of older indigenous Taiwanese women, we sought to compare the scores of fallers and non-fallers on four tests of physical performance. Additionally, we aimed to establish cutoff scores that would be discriminate fallers from nonfallers.

Methods: At baseline, study participants were evaluated using the Short Physical Performance Battery (SPPB), the Timed Up and Go (TUG) test, gait speed, and the Elderly Mobility Scale (EMS). Their falls were recorded monthly for the next 1 year, and individuals who fell at least once were classified as fallers. For each of the four tests, we estimated the area under the curve (AUC), as well as cutoff points and odds ratios (ORs) with confidence interval (CI) for falls.

Results: The study included 112 participants, with a mean (±standard deviation) age of 75.5 ± 6.2 years. Thirty-six (32%) of the participants were fallers. Except for the EMS, all tests had AUCs >0.8, as well as moderate sensitivities and specificities. The cutoff point for predicting being a faller were 10.5 for the SPPB (OR, 8.4; CI, 3.3–21.4), 13.9 s for the TUG test (OR, 19.4; CI, 6.9–55.1), 0.84 m/s for gait speed (OR, 8.9; CI, 3.6–22.0), and 19.5 for EMS (OR, 3.4; CI, 1.5–8.0).

Conclusion: The SPPB, TUG, and gait speed might provide effective means of fall screening among older indigenous Taiwanese women.

1. Introduction

In aging societies, falls among older adults are a serious social concern and public health issue, mainly because falls are strongly associated with loss of independence, institutionalization, and mortality.[1–3] Each of these outcomes poses a heavy burden on the families of affected individuals, and requires considerable governmental medical resources.[3,4]

Although it has been reported that the etiology of falls is multifactorial, intrinsic physical factors contribute substantially to falls among older adults.[2–5] Therefore, fall-related screening tools that are related to physical and balance functions have been developed for fall prevention among community-dwelling older adults.[1,5–7] However, to date, no report has specifically focused on indigenous older populations. Further, the selection of participants has varied across previous studies, which could limit the applicability of their results for community-dwelling older adults.[2,5,7]

In Taiwan and many developed countries, indigenous people have poorer health and more health needs than do nonindigenous people.[8–12] According to Council of Indigenous Peoples (CIP), the average life expectancy of community-dwelling indigenous people living in the remote areas of Taiwan was lower than that of other community-dwelling older adults.[8] Accident events, including falls, occur more often among indigenous older adults than among other community-dwelling older adults in Taiwan.[8] Although it has been noted that indigenous Taiwanese face high rates of healthy concerns and accident events, the incidence of falls and fall prevention-related screening tools have yet to be reported for the community-dwelling, older, indigenous Taiwanese population. On the other hand, previous studies have shown that women have higher risks of falls than men.[3,12,13] Moreover, older indigenous women have more higher fall risks than do older indigenous men in Taiwan.[14]

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Therefore, the present study of community-dwelling older indigenous Taiwanese women was undertaken for two purposes: First, we sought to investigate the actual incidence of falls during a 12-month follow-up period. Second, we aimed to apply common and easy-to-administer physical performance tests, and to determine cutoff scores and odds ratios (ORs) for predicting which individuals were fallers. The following four tests were investigated: the Short Physical Performance Battery (SPPB), the Timed Up and Go (TUG) test, gait speed, and the Elderly Mobility Scale (EMS).

2. Patients and methods

2.1. Participant selection

This study enrolled a convenience sample of female participants living in indigenous communities in Hsiu-Lin Township (Hualien County, Taiwan). Enrollment was conducted through local community centers, churches, and places of public assembly. The inclusion criteria were as follows: age $\geq$65 years, ability to follow the steps involved in the assessments/tests, and ability to ambulate independently (with or without a mobility aid). The exclusion criteria were as follows: severe heart disease, a history of nervous system disorders (such as stroke or Parkinson's disease) or severe orthopedic diseases that rendered the individuals unable to walk or stand even with an aid; hospital admission within 6 months.

In this study, a fall was defined as any accidental event that resulted in the person coming to rest on the ground, but not as a consequence of sustaining a violent blow, loss of consciousness, sudden onset of paralysis, alcoholic drink. Fall events were recorded on a “fall calendar” for 1 year by each participant or her family members, who were instructed to update the calendar daily. One therapist who was not involved in the study visited or called the participants at the end of every month. Participants with one or more fall events during the study year were assigned to the faller group, and the remaining participants assigned to the nonfaller group.

At the start of the study, the demographic characteristics of all participants were collected and four physical performance tests were subsequently conducted in a random order by an experienced physical therapist. Before performing each test, each participant was taught how the test was executed to minimize variation in test performance. The participant had one trial attempt to familiarize themselves with the procedure and was given a 1-min resting period between each pair of performance tests.

2.2. Physical performance tests

2.2.1. SPPB

The SPPB is a reliable and valid test for assessing lower extremity functional performance, and is one of the most frequently used physical performance tests for older adults. It consists of three major items: balance, five-repetition chair-stand, and gait speed. The test participant stands up from a seated position in a chair without using arm support for five repetitions, which are performed as quickly as possible and timed in seconds. Subsequently, the participant is given a balance test (from close feet to tandem position). Finally, the time that the participant needs to complete a 4-m walk test is recorded. Each item is scored on a 4-point scale, the possible range of total scores is 0–12, and higher scores indicate better function.[15,16]

2.2.2. TUG test

The TUG test is a screening tool that is commonly used to assist clinicians in identifying older adults who are at risk of falling. In this test, participants are timed while they stand up from a seated position in a chair with a seat height of 40–50 cm, walk a 3-m distance at a usual pace, turn, walk back to the chair, and finally sit down again.[17] In this study, two trials were performed with a 30-s interval, and the mean time of the two trials was considered the final score.

2.2.3. Gait speed

This study used a 10-m walk test with 5 m provided for acceleration/deceleration.[18] The participants used their self-selected walking pace with a 30-s interval between trials. The time that was taken to traverse the middle 10 m was averaged over two trials and used as the final score.

2.2.4. EMS

The EMS was designed for analyzing the following crucial functions associated with mobility: movement from a lying position to a sitting position, movement from a sitting position to a lying position, movement from a sitting position to a standing position, standing, gait, walking speed, and functional reach. The maximum score is 20, which represents independent mobility, whereas the minimum score is 0, which represents total dependence. A previous study reported that EMS scores showed high, significant correlations with Barthel scale scores and functional independence measure scores, thus establishing the concurrent validity of the EMS.[19]

The Research Ethics Committees of Tzu Chi General Hospital approved the study, and all participants provided informed consent prior to participation.

2.3. Statistical analysis

To assess the statistical significance of between-group differences in baseline data and performance outcomes, we used independent t tests for continuous data and chi-square tests for categorical data. To evaluate the intrarater test–retest reliability of the physical performance tests, 19 participants were retested within 2 weeks using the four physical performance tests, based on which intraclass correlation coefficients (ICCs) were estimated. To test the predictive powers of the tests, we calculated receiver operating characteristic (ROC) curves, estimated areas under the curves (AUCs), and used Youden's index to select cutoff points. We estimated the sensitivities and specificities of the four physical performance tests to investigate their performance as means of screening older indigenous Taiwanese women who were at high risk of falling.

Bivariate logistic regression was used to calculate the odds ratios (ORs) with 95% confidence intervals and the cutoff values of the 4 physical mobility tests for the faller group versus the nonfaller group. Variables with $p < 0.05$ in the bivariate analysis were entered into a multiple regression analysis. The variances inflation factor (VIF) was evaluated for multicollinearity. The significance level was set at 0.05 in all cases. Analyses were performed using SPSS Version 19.0 for Windows (SPSS Inc., Chicago, USA).

The sample size was estimated by using MedCalc software (MedCalc Software, Ostend, Belgium) and at least 81 participants would be needed to achieve a power of 0.8 at an alpha level of 0.05 for an AUC of at least 0.69.

3. Results

In total, 124 community-dwelling older indigenous Taiwanese women were enrolled and participated in the study. However, 12 participants were excluded because of 2 moved out to live with their children, 3 for institutionalization, 4 was lost contact, and 3 participants died. Ultimately, 112 participants (mean $\pm$ standard

deviation age, 75.5 ± 6.2 years) were collected and analyzed. Thirty-two percent of the women were categorized into the faller group. Table 1 presents that demographics did not differ significantly between the two groups and fallers exhibited significantly poorer performance than did nonfallers in all of the physical performance tests. The ORs, ranged from 3.4 to 19.4, corresponding to the selected cutoff points of logistic univariate analysis are shown in Table 1.

The ICCs of the four tests were excellent, ranging from 0.93 to 0.98. The VIFs among the four tests, ranging from 1.2 to 5.3, can be considered acceptable. Fig. 1 and Table 2 show the cutoff points of the four physical tests and their associated sensitivities and specificities for discriminating fallers from nonfallers. Sensitivities and specificities ranged from 60% to 91%, and the AUCs were ≥0.8 for all of the tests except the EMS, confirming satisfactory discriminative ability.[19] As Table 3, the SPPB (OR = 0.66; $p < 0.015$) in combination with TUG (OR = 1.22; $p < 0.04$) appears to be the best predictor of falls after a multivariate logistic regression analysis incorporating all the possible variables into the model.

4. Discussion

Our investigation showed a fall incidence of 32% and the value is slightly higher than that reported in studies of community-dwelling Chinese older people living in China, Hong Kong, Macao, Singapore and Taiwan, approximately to 18%.[14,17] However, the value is closed to Kwan et al.'s investigation, nearly to 33%.[20] The higher incidence of falls could be attributable to the following factors: First, accident events—including falls—occur more frequently among older indigenous Taiwanese adults.[8] Second, the health behaviors and lifestyles of community-dwelling indigenous people in remote or rural areas differed from those of community-dwelling older adults in urban areas, which might have presented higher risks of falls.[10,11,14] Third, older indigenous women had higher fall risk than did older indigenous men.[14] Fourth, the number of falls is known to increase with age.[1,2,6,12,13] Because the life expectancy of indigenous Taiwanese people is lower than that of the entire Taiwanese population (69 vs. 79 years),[8] the mean age of the participants in our study was 75.3 years, which suggests that the population was relatively old.

Regarding sensitivity, specificity and areas under the ROC curve among the 4 physical performance tests, the SPPB demonstrated the best discriminative power for fallers, followed by the TUG, then gait speed. After a multivariate regression analysis, the SPPB in combination with TUG appears to be the best predictive fall risk model. The SPPB has been used widely to predict subsequent disability and worsening mobility, and associated with injurious falls.[15,16,21] However, previous studies have not reported the SPPB as a means of falls screening in older indigenous adults. In the present study, the cutoff point for the SPBB was 10.5 (OR, 8.4) and the faller group attained a significantly lower SPPB score (7.6) than did the nonfaller group (11.0). Park et al reported that the SPPB of participants without any fall was 10.3 or greater,[22] which nearly equals the cutoff score that was found in our study. Furthermore, the definition of a fall and number of falls in their study were similar to our study. In contrast, the SPPB score in our faller group was lower than the value reported for their faller group (7.6 vs. 9.8) because the participants in Park et al.'s study[22] were younger than the participants in our study (69.4 vs. 75.3 years).

Although the TUG test has been recommended as a routine screening test for falls in the guidelines of the American Geriatric Society and the British Geriatric Society,[1] the role in predicting falls among community-dwelling older adults remains controversial.[23–26] Our report demonstrates that the TUG test can efficiently discriminate fallers from nonfallers among older indigenous Taiwanese adults. Our results support those of Lin et al,[17] who demonstrated that the TUG test has the largest AUC for predicting the occurrence of falls, and can efficiently determine the fall status of community-dwelling older adults in rural areas. The cutoff point (13.9 s) in the present study was closed to the findings of Shumway-Cook et al[23] but different from the results of other studies,[24–26] which could be explained by the following reasons. First, one must consider ethnic and living area differences in the physical functions of older adults. Second, our study included participants with chronic diseases. Both of these factors might have resulted in lower functional performance.[4,11,13,14] Third, it should also be noted that, unlike other studies,[7,24–26] we used a comfortable walking speed (rather than a faster speed) for the TUG test. Naturally, test results differ for comfortable and fast walking.[26] Furthermore, the TUG has greater value for discriminating fallers from nonfallers in populations of less healthy, lower-functioning older people, and its predictive ability and diagnostic accuracy are at best moderate.[25] Therefore, we thought that the cutoff point of 13.9 s could be efficiently discriminated fallers from nonfallers.

Gait speed has often been viewed as an index of fall risk,[1–3] and fallers demonstrate lower gait speed than do nonfallers. Menant et al reviewed 30 studies and reported that gait speed is useful for predicting falls in older adults, under either single-task or dual-task tests.[27] Our study suggest that, even with a single-task test, gait speed could be used as an assessment of fall risk in older indigenous Taiwanese women. The different walking speeds (fast or usual pace) and distances (4–10-m) in the gait speed test used in previous studies make comparison of results between studies more challenging.[18]

Table 1
Comparison of the demographics and the scores on 4 physical performance tests of the nonfaller and faller groups.

Variables	All (n = 112)	Nonfallers (n = 76)	Fallers (n = 36)	p value	OR	95% CI
Age (y)	75.3 ± 6.3	74.8 ± 6.7	76.4 ± 5.4	0.20		
Height (cm)	150.1 ± 5.5	150.6 ± 5.5	148.8 ± 5.2	0.09		
Weight (kg)	57.7 ± 9.9	58.1 ± 9.7	57.0 ± 10.5	0.63		
Body mass index	25.8 ± 4.0	25.6 ± 4.0	26.3 ± 4.3	0.38		
Hypertension	70 (62.5)	47 (61.8)	23 (63.9)	0.83		
Diabetes	24 (21.4)	15 (19.7)	9 (25.0)	0.53		
Heart disease	18 (16.1)	12 (15.8)	6 (16.7)	0.91		
Knee osteoarthritis	46 (41.1)	28 (36.8)	18 (50.0)	0.19		
Stroke	7 (6.3)	4 (5.3)	3 (8.3)	0.53		
SPPB	9.88 ± 2.76	10.99 ± 1.33	7.56 ± 3.48	<0.01	8.4*	3.3–21.4
TUG test (s)	11.88 ± 4.81	10.02 ± 2.55	15.82 ± 6.01	<0.01	19.4*	6.9–55.1
Gait velocity (m/s)	0.97 ± 0.32	1.08 ± 0.27	0.75 ± 0.28	<0.01	8.9*	3.6–22.0
EMS	18.59 ± 1.74	19.09 ± 1.25	17.56 ± 2.14	<0.01	3.4*	1.5–8.0

Abbreviations: CI, confidence interval; EMS, Elderly Mobility Scale; OR, odds ratio; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go.
Continuous values are presented as means ± standard deviations. Categorical variables are presented as n (%). *$p < 0.05$.

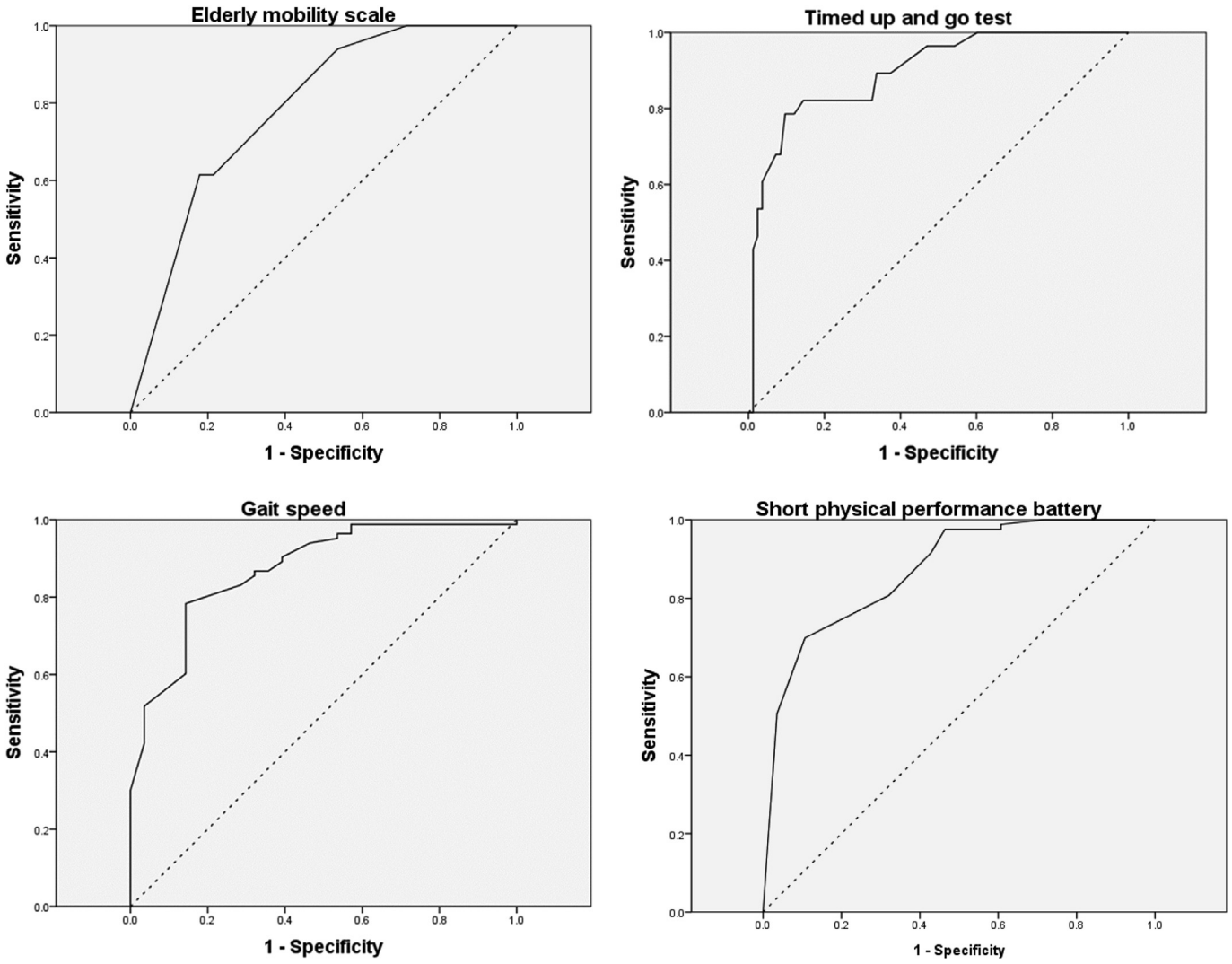

Fig. 1. Receiver operating characteristic curves for the four physical performance tests.

Table 2
Cutoff points for scores on the four physical performance tests, and the associated sensitivities, specificities, and areas under the curves.

Variables	Cutoff point	Sensitivity	Specificity	AUC (95% CI)
SPPB	10.5	0.71	0.78	0.82 (0.73–0.91)
TUG test (s)	13.9	0.92	0.64	0.81 (0.72–0.91)
Gait velocity (m/s)	0.88	0.76	0.72	0.81 (0.72–0.90)
EMS	19.5	0.61	0.69	0.71 (0.60–0.82)

Abbreviations: AUC, area under the curve; CI, confidence interval; EMS, Elderly Mobility Scale; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go.

Table 3
Risk model for fall prediction obtained by multiple logistic regression.

	B	SE	*p* value	OR	95% CI
TUG	0.20	0.10	0.04	1.22	1.01–1.47
SPPB	−0.41	0.17	0.015	0.67	0.48–0.92
Constant	0.82	2.51	0.744	2.28	

Abbreviations: B, regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go.

The EMS is used to evaluate general balance, as well as transfer and locomotion abilities, which represent basic physical mobility and are prerequisites to more complex ADLs.[19] However, the cutoff point was 19.5 in this study seemly causes a ceiling effect.[19] This could be attributable to a certain degree of heterogeneity in our participants and approximately 50% of our participants scored 20 points on the EMS. Another, it is possible that the inclusion criteria were not sufficiently robust. Indeed, we included women with and without chronic diseases, only requiring that they had independent walking ability with or without walking aids.

4.1. Limitations

There are several limitations to our study. First, we did not divide the faller group into single fallers and more frequent fallers, which limits the generalizability of our results and may have resulted in overestimation of the predictive value of the four physical performance tests for falls. However, due to medical health resource inconvenient and in-accessibility for people living in remote area, it could be the best strategy for the prevention better than cure. Second, the sample was not representative of all older indigenous women in Taiwan, since the Plains and Mountain tribes

are both officially recognized by the CIP. Third, even with a falls diary, few participants or family members were unable to given us the correct date when the participants had a fall leading to some uncertainties about the validity and reliability of self-reported falls. Fourth, we did not investigate the fall history, medication use and depression, which could influence the incidence of falls and bias our results.[13,20]

5. Conclusion

In this study, the incidence of falls among older indigenous Taiwanese women was 32%. The following cutoff scores were identified for the four investigated physical performance tests: 10.5 for the SPPB, 13.9 s for the TUG test, 0.84 m/s for gait speed, and 19.5 for the EMS. We hope that the SPPB, TUG, gait speed tests may serve as references for falls-related screening of indigenous Taiwanese women. In addition, the SPPB in combination with TUG appears to be the best predictive role for falling.

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References

1. American Geriatrics Society, British Geriatrics Society, American Academy of Orthopaedic Surgeons Panel on Falls Prevention. Guideline for the prevention of falls in older persons. *J Am Geriatr Soc*. 2001;49:664–672.
2. Rubenstein LZ. Falls in older people: epidemiology, risk factors and strategies for prevention. *Age Ageing*. 2006;35(suppl 2):ii37–ii41.
3. Todd C, Skelton D. *What Are the Main Risk Factors for Falls Among Older People and what Are the Most Effective Interventions to Prevent These Falls?*. WHO Regional Office for Europe; 2004. Available at: http://www.euro.who.int/__data/assets/pdf_file/0018/74700/E82552.pdf. Accessed 11 November 2016.
4. Demura S, Kasuga K, Sato S, et al. Determination of persons at a high risk of falling in a population of healthy community-dwelling elderly Japanese. *Int J Gerontol*. 2013;7:13–16.
5. Tiedemann A, Shimada H, Sherrington C, et al. The comparative ability of eight functional mobility tests for predicting falls in community-dwelling older people. *Age Ageing*. 2008;37:430–435.
6. Ganz DA, Bao Y, Shekelle PG, et al. Will my patient fall? *JAMA*. 2007;297:77–86.
7. Gates S, Smith LA, Fisher JD, et al. Systematic review of accuracy of screening instruments for predicting fall risk among independently living older adults. *J Rehabil Res Dev*. 2008;45:1105–1116.
8. CIP-Council of Indigenous Peoples. *Statistical Data of Aboriginal Population*. Taipei, Taiwan: CIP; 2016. Available at: http://www.apc.gov.tw/portal/docDetail.html?CID=940F9579765AC6A0&DID=0C3331F0EBD318C227FDA056D70DFF76. Accessed 13 Septemper 2016.
9. Statistics Canada. *2011 National Household Survey: Data Tables*. Ontario, Can: Statistics Canada; 2011. Available at: https://www12.statcan.gc.ca/nhs-enm/2011/dp-pd/dt-td/Index-eng.cfm. Accessed 15 November 2016.
10. Gubhaju L, McNamara BJ, Banks E, et al. The overall health and risk factor profile of Australian Aboriginal and Torres Strait Islander participants from the 45 and Up study. *BMC Public Health*. 2013;13:661.
11. Gubhaju L, Banks E, MacNiven R, et al. Physical functional limitations among aboriginal and non-aboriginal older adults: associations with Socio-Demographic factors and health. *PloS One*. 2015;10(9):e0139364. http://dx.doi.org/10.1371/journal.pone.0139364.
12. Delbaere K, Van den Noortgate N, Bourgois J, et al. The physical performance test as a predictor of frequent fallers: a prospective community-based cohort study. *Clin Rehabil*. 2006;20:83–90.
13. Kwan MM, Close JC, Wong AK, et al. Falls incidence, risk factors, and consequences in Chinese older people: a systematic review. *J Am Geriatr Soc*. 2011;59:536–543.
14. Lee LL, Lin SH, Philp I. Health needs of older aboriginal people in Taiwan: a community-based assessment using a multidimensional instrument. *J Clin Nurs*. 2015;24:2514–2521.
15. Guralnik JM, Ferrucci L, Simonsick EM, et al. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med*. 1995;332:556–561.
16. Freiberger E, de Vreede P, Schoene D, et al. Performance-based physical function in older community-dwelling persons: a systematic review of instruments. *Age Ageing*. 2012;41:712–721.
17. Lin MR, Hwang HF, Hu MH, et al. Psychometric comparisons of the timed up and go, one-leg stand, functional reach, and Tinetti balance measures in community-dwelling older people. *J Am Geriatr Soc*. 2004;52:1343–1348.
18. Peters DM, Fritz SL, Krotish DE. Assessing the reliability and validity of a shorter walk test compared with the 10-meter walk test for measurements of gait speed in healthy, older adults. *J Geriatr Phys Ther*. 2013;36:24–30.
19. Chiu AY, Au-Yeung SS, Lo SK. A comparison of four functional tests in discriminating fallers from non-fallers in older people. *Disabil Rehabil*. 2003;25:45–50.
20. Kwan MM, Lin SI, Close JC, et al. Depressive symptoms in addition to visual impairment, reduced strength and poor balance predict falls in older Taiwanese people. *Age Ageing*. 2012;41:606–612.
21. Ward RE, Leveille SG, Beauchamp MK, et al. Functional performance as a predictor of injurious falls in older adults. *J Am Geriatr Soc*. 2015;63:315–320.
22. Park JH, Cho H, Shin JH, et al. Relationship among fear of falling, physical performance, and physical characteristics of the rural elderly. *Am J Phys Med Rehabil*. 2014;93:379–386.
23. Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go test. *Phys Ther*. 2000;80:896–903.
24. Schoene D, Wu SM, Mikolaizak AS, et al. Discriminative ability and predictive validity of the timed up and go test in identifying older people who fall: systematic review and meta-analysis. *J Am Geriatr Soc*. 2013;61:202–208.
25. Barry E, Galvin R, Keogh C, et al. Is the Timed Up and Go test a useful predictor of risk of falls in community dwelling older adults: a systematic review and meta-analysis. *BMC Geriatr*. 2014;14:14.
26. Kamide N, Takahashi K, Shiba Y. Reference values for the Timed Up and Go test in healthy Japanese elderly people: determination using the methodology of meta-analysis. *Geriatr Gerontol Int*. 2011;11:445–451.
27. Menant JC, Schoene D, Sarofim M, et al. Single and dual task tests of gait speed are equivalent in the prediction of falls in older people: a systematic review and meta-analysis. *Ageing Res Rev*. 2014;16:83–104.