ABSTRACT

Objectives Regular moderate-to-vigorous intensity recreational physical activity (PA) improves physical and cognitive functions. However, the age-associated relationships between non-recreational PA and functional ability remain less explored. We examined the associations between housework and functional health among younger and older Singaporean community-dwelling adults.

Methods Light housework (LH) and heavy housework (HH) were dichotomised into low- and high-volume and occupational and transport-related PAs were assessed using PA questionnaires. Participants were recruited from a large residential town in Singapore.

Results Among older but not younger adults, RBANS scores were 8% and 5% higher in high HH and LH groups compared with low HH and LH groups, respectively (p=0.012 and p=0.016). Specifically, HH was associated with 14% higher attention score (p=0.014), and LH was associated with 12% and 8% higher immediate and delayed memory scores, respectively (p<0.001 and p=0.004). In older adults, sit-to-stand time and PPA scores were 8% and 23% lower in the high HH group than the low HH group, respectively (p=0.011 and p=0.040). SPPB and gait speed did not differ with age or HH. LH was not associated with physical or sensorimotor function.

Conclusions Among older adults, housework is associated with higher cognitive function, specifically in attention and memory. Associations of housework with physical function and sensorimotor performance were intensity dependent. Housework PA is positively associated with functional health among community-dwelling older adults, independent of recreation and other non-recreational PAs. Further longitudinal and intervention studies are needed to establish causality.

INTRODUCTION

Regular physical activity (PA) improves physical and mental health, mitigates the risks and effects of chronic diseases, and reduces falls, immobility, dependency and mortality among older adults.1–3 Yet, global surveillance data indicate that in 2016, levels of insufficient PA remained high (27.5%) and stable across the previous 10 years.4 The prevalence of insufficient PA was also more than double in high-income countries than in low-income countries (36.8% vs 16.2%), and was the highest in Singapore (36.5%) among high-income Asia Pacific countries.4 In wealthier countries, transition towards more sedentary occupations and motorised transportation could explain the higher levels of inactivity. The majority of PAs in high-income countries are from recreational PA, which differed...
from low-income countries where PA is predominantly from non-recreational activities, including transportation, occupational and housework.\textsuperscript{13} Given the increasing prevalence of insufficient PA globally,\textsuperscript{6} better strategies and policies are required to increase PA levels, especially among older adults, due to their increased vulnerability to adverse health outcomes.\textsuperscript{6}

Earlier studies in high-income countries largely focused on the effects of recreational PA on physical and cognitive capacities, which are key risk factors for falls among older adults.\textsuperscript{7,8} Few studies have examined the independent effects of non-recreational activity, such as housework tasks, on age-associated decline in functional ability.\textsuperscript{10-12} Furthermore, although the effects of exercise intensity have been widely investigated,\textsuperscript{1} none of the studies investigated the associations between housework intensity and age-associated functional health. With the rapidly ageing population and increasing life expectancy worldwide, approaches to promote healthy ageing, which centres on the maintenance of functional ability, are urgently needed.\textsuperscript{13}

Housework activities are a large part of everyday activities in older people and account for a significant proportion of self-reported PA.\textsuperscript{11} Apart from a meaningful occupation, housework is also a component of instrumental activities of daily living—both key factors of successful ageing. Additionally, single bout of housework and chronic housework are associated with improved cognition, brain volume and executive function, and negatively associated with frailty.\textsuperscript{10-12} Regardless of country income levels, higher levels of non-recreational PA were associated with a graded reduction in mortality and cardiovascular diseases, suggesting the potential role of non-recreational PA, such as housework, on improving health outcomes even in high-income countries.\textsuperscript{8} Housework may also confer benefits on physical and mental functions among older adults in a high-income country such as Singapore. Therefore, we studied the associations of light housework (LH) and heavy housework (HH) activities with cognitive, physical and sensorimotor functions, among younger and older adults in Singapore.

\textbf{METHODS}

\textbf{Settings}

Community-dwelling adults (≥21 years) were recruited from a large, northeastern residential town of Yishun in Singapore, with residential population of 220,320 (50.6% women), with 12.2% older adults (≥65 years). This is similar to the overall Singapore residential population of 4,044,200 (51.1% women), with 15.2% older adults (≥65 years).\textsuperscript{15}

\textbf{Participants}

Participants were recruited cross-sectionally from the Yishun Study through random sampling, in quotas of 20–40 participants in each sex and age group (10-year age groups between 21 and 60 years old and 5-year age groups after 60 years), to obtain a representative sample of ~300 men and ~300 women.\textsuperscript{16} Briefly, community-dwelling adults aged 21 years and above who were independent in performing activities of daily living, had <5 comorbidities and had no neuromuscular or cognitive disorders were recruited. Those between 21 and 64 years and between 65 and 90 years of age were categorised as younger and older participants, respectively. Participants self-reported their years of education and medical conditions and comorbidities. All assessments were based on standardised protocols and administered by trained researchers at the Geriatric Education & Research Institute Lab on Yishun Health Campus, mostly within one visit.

\textbf{Patient and public involvement}

Neither patients nor the public were involved in the design, planning, conduct or reporting of this study.

\textbf{Anthropometric assessment}

Body weight and height were measured using an electronic scale and stadiometer, respectively (SECA, Hamburg, Germany). Body mass index was calculated as body weight (kg) divided by height (m) squared.

\textbf{Housework and recreational, transport and occupational PAs}

Data on housework were self-reported and collected according to the Longitudinal Ageing Study Amsterdam Physical Activity Questionnaire (LAPAQ),\textsuperscript{17} which consists of specific questions regarding frequency and time spent on light and heavy household tasks. LH tasks included washing the dishes, dusting, making the bed, doing the laundry, hanging out the laundry, ironing, tidying up and cooking meals. HH tasks included window cleaning, changing beddings, beating the mat, vacuuming, washing or scrubbing the floor, and chores involving sawing, carpeting, repairing or painting. The median time spent per week on household activities was used to dichotomise participants into high and low groups for LH (315 min/week) and HH (15 min/week) groups. LH was assigned a metabolic equivalent of task (MET) of 2.5 and HH was assigned a MET of 4.0.\textsuperscript{18}

Recreational (sport, fitness or leisure time activities), transport (active commuting/travel) and occupational (work) PAs were determined using the Global Physical Activity Questionnaire (GPAQ), which consists of questions assessing the frequency and duration of vigorous-intensity or moderate-intensity activities during a typical week.\textsuperscript{19} A cut-off of ≥600 MET min/week (≥150 min/week of moderate-intensity PA or ≥75 min/week of vigorous-intensity PA) was used to determine the percentage of participants who met the current PA guidelines.\textsuperscript{5,20}

\textbf{Cognitive function}

Cognitive performance was assessed by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score. RBANS is a standardised age-adjusted battery that is sensitive to cognitive impairment.\textsuperscript{21} RBANS assesses global and specific cognitive domains including...
immediate and delayed memories, visuospatial construction, language and attention.

Physical function
Habitual gait speed was assessed using a 6 m GAITRite Walkway (CIR Systems, Sparta, New Jersey, USA) with 2 m lead in and out phase. Participants performed three trials and the average timing was recorded. The Short Physical Performance Battery (SPPB) consists of three subtests including balance, gait and sit-to-stand.\(^2\)\(^2\) The balance subtest is composed of three parts with progressive difficulty, including unaided feet-together stand, semitandem stand and full-tandem stand. Participants were timed until they moved or 10 s elapsed time. Gait speed was assessed by participants walking 8 ft at their usual pace, with a moving start.\(^2\)\(^2\) The average timing was recorded over two trials. To assess sit-to-stand time, participants folded their arms across their chest and performed five chair stands as quickly as possible. Each of the three subtests was scored from 0 to 4, and the total score was the sum of three subtests, ranging from 0 to 12. Higher SPPB scores indicated better physical function.\(^2\)\(^2\)

Sensorimotor or physiological falls risk assessments
Physiological falls risk was determined using the Physiological Profile Assessment (PPA) short version, which has been shown to predict fall incidents and consists of five validated sensorimotor measures: visual contrast sensitivity, hand reaction time, knee extension strength, proprioception and postural sway.\(^2\)\(^4\)\(^5\) The five measures were weighted to compute a composite PPA index score using the NeuRA FallScreen Falls Risk Calculator (https://fbirc.neura.edu.au/fallscreen). Higher PPA scores indicate poorer sensorimotor performance and greater falls risk.\(^2\)\(^4\)\(^5\)

Statistical analysis
All statistical analyses were performed using R V.3.6.2 (R Foundation for statistical computing, Vienna, Austria). A sample size of 400 (100 per group) was needed for the trial to have 80% power to detect a two-sided hypothesis test at an α level of 0.05 (effect size of 0.2) (G*Power, V.3.1, Germany). All participants with completed outcome measures were included for analysis. Numerical variables are presented as mean (SD) in text and figures unless otherwise stated. Participant characteristics were analysed using independent samples t-test to assess potential differences between high and low HH and LH groups. Sensorimotor, cognitive and physical function measures were analysed using two-way analysis of variance for HH and LH independently, with age group (younger vs older), housework groups (low vs high) and their interaction (age×housework) as fixed effects. Normality and homogeneity of variances assumptions were tested using Shapiro-Wilk and Levene tests, respectively. Effect sizes are reported with partial eta squared (\(\eta^2\)).\(^2\)\(^6\) A p value of <0.05 was considered statistically significant.

RESULTS
Participant characteristics
A total of 249 participants (57% women) with mean age of 44 years (SD 14 years) in the younger group, and 240 participants (57.1% women) with mean age of 75 years (SD 6 years) in the older group, had housework (LAPAQ) data available and were included in the analysis. Ethnic distribution of participants (82.0% Chinese, 8.4% Malay, 6.7% Indians and 2.9% from other ethnicities) was similar to that of Singapore’s population.\(^1\)\(^5\) A total of 36% (n=90) and 48% (n=116) of the participants in the younger and older groups, respectively, met the recommended PA level derived exclusively from recreational PA.\(^2\)\(^0\) These values were lower than 61% (n=152) and 66% (n=159) of the younger and older participants, respectively, who attained the recommended PA level exclusively through housework activities.

Participant demographics between high and low HH and LH groups, such as age, education, anthropometric, PA and housework data, are summarised in table 1. Compared with low HH and LH groups, majority of participants in high HH and LH groups were women, regardless of age groups. Within the younger group, those in the high LH group were shorter and had less years of education than those in the low LH group (all p<0.001, table 1). Total, recreational and occupational PAs did not differ between high and low HH and LH groups in younger and older adults (all p>0.05, table 1). Within the younger but not the older group, transport-related PA was 39% lower in the low LH group than in the high LH group (p=0.003, table 1). Regardless of age group, compared with low HH and LH groups, participants in the high HH and LH groups spent more time on both LH and HH activities per week and had higher total housework MET min/week (all p<0.001, table 1).

For subsequent LH analyses, age, sex, height, education, transport PA and HH were included in the model to adjust for confounding variables. To adjust for confounding factors, age, sex and LH were included in the model for subsequent HH analyses. Adjusting for recreational and occupational PAs in the analyses did not affect any of the results presented; hence, data are presented with recreational and occupational PAs excluded from the model.

Associations of HH activities with cognitive function
Within the older group, RBANS global cognition score was 8% higher in the high HH group than in the low HH group (p=0.012) but did not differ between high and low HH groups among the younger individuals (p=0.630) (age×housework; p=0.031, \(\eta^2\)\(_p\)=0.01; figure 1A). Immediate memory index scores between high and low HH groups were not statistically significant among older (p=0.055) and younger adults (p=0.332),...
despite significant interaction effects (age×housework; p=0.038, \( \eta^2_p = 0.009 \); figure 1B). No significant interaction effects between age and HH groups were observed for delayed memory (p=0.108, \( \eta^2_p = 0.005 \)), visuospatial construction (p=0.183, \( \eta^2_p = 0.004 \)) and language index scores (p=0.776, \( \eta^2_p = 0.0002 \)) (figure 1C–E). Attention index score was 14% higher in the high HH than in the low HH group within the older group (p=0.014) but not within the younger group (p=0.304) (age×housework; p=0.012, \( \eta^2_p = 0.01 \); figure 1F).

**Associations of LH activities with cognitive function**

Compared with the low LH group, the high LH group had 5% higher RBANS global cognition score among the older but not the younger adults (p=0.016 vs p=0.335) (age×housework; p=0.015, \( \eta^2_p = 0.01 \); figure 2A). Within

| Table 1 | Mean (SD) participant characteristics for high and low HH and LH groups, within younger and older groups |
|----------------|---------------------------------------------------------------|
|               | HH Low | HH High | P value | LH Low | LH High | P value |
| Younger        |        |         |         |        |         |         |
| n              | 100    | 149     |         | 137    | 112     |         |
| Sex, female, n (%) | 48 (48) | 94 (63) |         | 62 (45) | 80 (71) |         |
| Age (years)    | 43 (15) | 44 (13) | 0.516   | 42 (14) | 46 (13) | 0.015   |
| Education (years) | 12 (4) | 12 (4)  | 0.493   | 13 (4) | 11 (4)  | <0.001  |
| Height (m)     | 1.64 (0.09) | 1.62 (0.08) | 0.115 | 1.65 (0.08) | 1.60 (0.08) | <0.001 |
| Weight (kg)    | 68.0 (15.2) | 67.7 (17.3) | 0.875 | 69.0 (17.2) | 66.4 (15.5) | 0.219   |
| Body mass index | 25.2 (4.8) | 25.6 (5.6) | 0.557 | 25.1 (5.4) | 25.8 (5.2) | 0.324   |
| PA (GPAQ)      |         |         |         |        |         |         |
| Recreational (MET min/week) | 576 (784) | 774 (1302) | 0.137 | 637 (933) | 764 (1324) | 0.393   |
| Transport (MET min/week) | 2065 (3010) | 2003 (2228) | 0.861 | 1577 (1955) | 2579 (3075) | 0.003   |
| Occupational (MET min/week) | 1686 (3619) | 2408 (5658) | 0.220 | 2052 (4252) | 2199 (5699) | 0.821   |
| Total (MET min/week) | 4327 (5151) | 5185 (6903) | 0.263 | 4266 (4971) | 5543 (7511) | 0.125   |
| Housework activity (LAPAQ) |         |         |         |        |         |         |
| Heavy (min/week) | 0 (2) | 192 (292) | <0.001 | 47 (81) | 198 (335) | <0.001   |
| Light (min/week) | 198 (363) | 584 (593) | <0.001 | 95 (87) | 838 (592) | <0.001   |
| Total (MET min/week) | 496 (908) | 2228 (2079) | <0.001 | 425 (458) | 2887 (2120) | <0.001   |
| Older           |        |         |         |        |         |         |
| n              | 132    | 108     |         | 103    | 137     |         |
| Sex, female, n (%) | 63 (48) | 74 (69) |         | 39 (38) | 98 (72) |         |
| Age (years)    | 77 (6) | 73 (6)  | <0.001  | 77 (7) | 74 (6)  | 0.004   |
| Education (years) | 6 (4) | 7 (5)  | 0.168   | 7 (5) | 7 (5)  | 0.764   |
| Height (m)     | 1.57 (0.09) | 1.57 (0.08) | 0.987 | 1.58 (0.08) | 1.56 (0.08) | 0.064   |
| Weight (kg)    | 60.1 (10.3) | 58.5 (9.6) | 0.192 | 60.4 (9.8) | 58.6 (10.1) | 0.161   |
| Body mass index | 24.5 (3.7) | 23.8 (3.3) | 0.102 | 24.2 (3.5) | 24.1 (3.5) | 0.778   |
| PA (GPAQ)      |         |         |         |        |         |         |
| Recreational (MET min/week) | 828 (1053) | 890 (1047) | 0.650 | 867 (1181) | 847 (941) | 0.884   |
| Transport (MET min/week) | 1561 (1565) | 1836 (2050) | 0.253 | 1554 (1964) | 1783 (1667) | 0.340   |
| Occupational (MET min/week) | 676 (2269) | 401 (1397) | 0.251 | 547 (2113) | 557 (1783) | 0.968   |
| Total (MET min/week) | 3065 (2731) | 3127 (2531) | 0.856 | 2968 (2968) | 3187 (2366) | 0.537   |
| Housework activity (LAPAQ) |         |         |         |        |         |         |
| Heavy (min/week) | 0 (0) | 131 (140) | <0.001 | 31 (72) | 80 (134) | <0.001   |
| Light (min/week) | 446 (508) | 684 (568) | <0.001 | 89 (93) | 902 (485) | <0.001   |
| Total (MET min/week) | 1116 (1270) | 2236 (1584) | <0.001 | 347 (377) | 2576 (1349) | <0.001   |

Significant p values are indicated by bold typeface.

GPAQ, Global Physical Activity Questionnaire; HH, heavy housework; LAPAQ, Longitudinal Ageing Study Amsterdam Physical Activity Questionnaire; LH, light housework; MET, metabolic equivalent of task; PA, physical activity.
Lee SY, et al. BMJ Open 2021;11:e052557. doi:10.1136/bmjopen-2021-052557

the older but not the younger individuals, immediate and delayed memory index scores were also 12% (p<0.001 vs p=0.165) and 8% (p=0.004 vs p=0.729) higher in high LH group than the low LH group, respectively (age×housework; p<0.001, $\eta^2_p=0.03$ and p=0.022, $\eta^2_p=0.01$; figure 2B,C). No significant interaction effects between

**Figure 1** Mean (SD) of (A) global cognitive function and specific domains, including (B) immediate memory, (C) delayed memory, (D) visuospatial-construction, (E) language and (F) attention, between high and low heavy housework groups, within younger and older adults. *P<0.05, adjusted for age, sex and time spent on light housework per week. RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

**Figure 2** Mean (SD) of (A) global cognitive function and specific domains, including (B) immediate memory, (C) delayed memory, (D) visuospatial-construction, (E) language and (F) attention, between high and low light housework groups, within younger and older adults. *P<0.05, **P<0.01, ***P<0.001, adjusted for age, sex, height, years of education, transport-related physical activity and time spent on heavy housework per week. RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.
age and LH groups were observed for visuospatial construction (p=0.781, $\eta^2_p=0.0002$), language (p=0.318, $\eta^2_p=0.002$) and attention (p=0.194, $\eta^2_p=0.004$) index scores (figure 2D–F).

**Associations of heavy housework activities with physical and sensorimotor functions**

The interaction effects between age and HH groups were not significant for total SPPB score (p=0.155, $\eta^2_p=0.004$; figure 3A) and gait speed (p=0.482, $\eta^2_p=0.001$; figure 3B). Within the older but not the younger group, sit-to-stand time was 8% lower in the high HH group than the low HH group (p=0.011 vs p=0.722) (age×housework; p=0.036, $\eta^2_p=0.009$; figure 3C). PPA index score, indicative of sensorimotor function, was 23% lower in the high HH group than in the low HH group, among the older (p=0.040) but not the younger adults (p=0.477) (age×housework; p=0.046, $\eta^2_p=0.008$; figure 3D).

**Associations of LH activities with physical and sensorimotor functions**

The interaction effects between age and LH groups were not significant for total SPPB score (p=0.709, $\eta^2_p=0.0003$), gait speed (p=0.136, $\eta^2_p=0.005$), sit-to-stand (p=0.445, $\eta^2_p=0.001$) (figure 4A–C). PPA index scores, indicative of sensorimotor function, were not significant between high and low LH groups among older (p=0.067) and younger adults (p=0.178), despite significant interaction effects (age×housework; p=0.021, $\eta^2_p=0.01$; figure 4D).

**DISCUSSION**

The present study is the first to report that housework activity is associated with cognitive, physical and sensorimotor functions among older but not younger adults in Singapore. These positive associations of housework with functional performance in older adults were independent of recreational, occupational and transport-related PAAs. We also show that more adults attained recommended PA levels through housework than recreation.

Regardless of intensity, higher levels of housework activities were associated with higher global cognition, among our population of older adults. Earlier studies observed that lower levels of housework activities were associated with mild cognitive impairment, cognitive decline and lower grey matter volume among older adults, suggesting a positive association between housework activities and cognitive function, plausibly through an increase in brain volume, as observed with exercise interventions in older adults. However, the positive associations...
between housework and cognition were not apparent in younger adults in our population. Differences in years of education between younger and older adults likely explain the disparity, as younger adults in this study had five more years of education on average than older adults. Since education level is positively associated with baseline cognitive function and slower cognitive decline, it is plausible that higher education levels and cognitive function in younger adults decrease the potential for better cognitive function associated with housework activities.

Our results demonstrate, for the first time, that the intensity of housework was differentially associated with specific cognitive domains. Heavy housework was associated with higher scores in the attention domain, while LH was associated with higher scores in both delayed and immediate memory domains in older adults. Earlier studies reported that aerobic exercise interventions of varying intensities improved specific cognitive function domains, including executive and motor function, attention and memory, through an increase in hippocampal volume and brain-derived neurotrophic factor expression. Given that housework accounted for a significant proportion (~24% to 36% in women and ~19% to 28% in men) of self-reported moderate-to-vigorous-intensity PA among older adults aged above 60, it is plausible that the higher cognitive function associated with housework occurs through a similar mechanism as PA or exercise. More studies are required to understand the underlying mechanisms driving the age-associated differing associations of housework intensity with specific cognitive domains.

Poorer cognitive performance in attention and executive functions were associated with poorer physical function, slower gait, postural instability and future falls among community-dwelling older adults. We show that higher levels of heavy housework activities were also independently associated with better physical function (chair-stand time) and sensorimotor (PPA) performance in older but not younger adults. Among older Swedish adults, longer chair-stand time and poorer cognitive performance (processing speed and executive function) independently increased the risk of injurious falls over 3–10 years by 10%–23%. Unlike older adults, younger adults have higher functional abilities and are unlikely to experience decline in sensorimotor and physical functions, potentially explaining the lack of associations between housework activities and physical and sensorimotor performances. These results collectively suggest that the higher cognitive, physical and sensorimotor functions related to heavy housework activities might plausibly be associated with lower physiological fall risk among community-dwelling older adults.

We demonstrated that unlike heavy housework, LH was not associated with physical or sensorimotor function. The lack of associations could be due to the already high functional ability of our study participants. In support, compared with lower intensity exercise, greater improvements in functional ability and decreased fear of falling were observed after high-intensity exercise in older adults. These results indicate a dose-response effect for exercise intensity on physical and sensorimotor functions and associated falls risk in older adults. Similarly, we propose that the positive associations of housework with physical and sensorimotor functions are dependent on intensity, especially in community-dwelling older adults.

Notably in this present study, 25% and 18% more participants in the younger and older groups, respectively, met the PA guidelines derived exclusively from housework, than that attained solely through recreational PA. This finding reflects the challenges inherent with recreational PA participation, which is, by definition, done during discretionary hours of the day outside of occupational and domestic duties. Incorporating PA into daily lifestyle through domestic duties (ie, housework) has the potential to achieve higher PA, which is positively associated with functional health especially among older community-dwelling adults.

Our study recruited adults aged 21–80+ randomly from a large residential town representative of Singapore’s population, suggesting a good degree of generalisability. We also included a comparison between older and younger adults in the study, to elucidate the age-associated effects of housework activities on cognitive, physical and sensorimotor functions. However, although associations can be drawn from the study results, the cross-sectional design does not prove causality. It is plausible that healthier older adults with higher functional ability engaged in higher levels of housework. Nonetheless, in a 13-year follow-up study, productive housework activities such as cooking and shopping were associated with lower mortality risk in older adults, suggesting that housework activities are associated with better health outcomes in older adults. Another potential limitation included the lack of patient or public involvement in the design, planning, conduct or reporting of the study. The study findings in community-dwelling individuals cannot be generalised to institutionalised older adults, such as those in nursing homes. In the present study, housework and PA measures were self-reported based on type, intensity, frequency and duration per week. Although the LAPAQ and GPAQ used in this study is valid and reliable, future studies using more objective measures of housework and PA should be undertaken. It is possible that socioeconomic status may mediate the effects of housework on health, which should be further examined in the Asian cultural context. While we adjusted for sex in all analyses, compared with low housework groups, participants in high housework groups were mostly women, which is consistent with earlier studies showing greater involvement in household chores among women than men. Future studies should investigate the sex-specific effects of housework on functional health.

In conclusion, our study suggests that a combination of light and heavy housework is associated with higher cognitive function, specifically in attention and memory domains, among community-dwelling older adults.
adults. Furthermore, the positive associations of housework levels with physical and sensorimotor functions in older adults were intensity dependent. Housework may also complement recreational PAs among current older community-dwelling adults in high-income countries towards healthier ageing. Future longitudinal and intervention studies are required to establish causality between housework activities and functional health.

Acknowledgements The authors gratefully acknowledge the strong support of Professor Pang Weng Sun in making this Yishun Study possible, and the support of Daniella Ng, Queenie Tan, Dr Lilian Chye, Sylvia Ng Siew Ching, Aziurrah Mohamed Ali, Mary Ng Pei Ern, Chua Xing Ying and Shermaine Thein in this study.

Contributors SYL performed the data analysis, interpretation and visualisation and wrote the manuscript. S-LW, TPN, BWJP and LKL contributed to the study concept and design. BWJP, LKL, KAJ, WTS and KKC administered the project and collected the data. BWJP and LKL accessed and verified the underlying data. S-LW and TPN contributed to the critical revision of the manuscript for important intellectual content. S-LW is responsible for the overall content as guarantor. All authors read and approved the final manuscript.

Funding This work was supported by Geriatric Education and Research Institute intramural funding (grant number GERI 1609).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by an ethics committee or institutional board (National Healthcare Group DSRB 2017/00212), in accordance with the relevant guidelines from the Declaration of Helsinki and the ethical principles in the Belmont Report. All participants gave written informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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