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Neighborhood environment, social participation, and physical activity in older adults with lower limb osteoarthritis: A mediation analysis

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ABSTRACT

Older adults with lower limb osteoarthritis (LLOA) are highly dependent on their physical and social environment for being physically active. Longitudinal data from 2286 older adults ($M_{age} = 73.8$ years; 50.3% female) in six European countries were analyzed using cross-lagged Structural Equation Modeling (SEM) and multi-group SEM. In cross-sectional analyses, neighborhood resources were associated with physical activity ($r = 0.26; p < .001$) and social participation ($r = 0.13; p = .003$). Physical activity at follow-up was associated with neighborhood resources, with this relationship mediated by social participation in people with LLOA ($\beta = 0.018; p = .013$). To promote future physical activity, opportunities to socially engage in neighborhoods need to be targeted primarily to people with LLOA.

1. Introduction

The health benefits of a physically active lifestyle are well-established in older adults with osteoarthritis, which is one of the most common musculoskeletal chronic health conditions (Andersson, 2008; Vina and Kwok, 2018). Regular physical activity is highly

recommended as a non-pharmacologic strategy for treating lower limb osteoarthritis (LLOA; i.e., clinical osteoarthritis in the knee and/or the hip) (Hochberg et al., 2012). Although older adults with osteoarthritis are encouraged to engage in modest intensity physical activity (Kraus et al., 2018; Osthoff et al., 2018), their physical activity levels are remarkably lower than those of older adults without the condition

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(Herbolzheimer et al., 2016).

The physical and social environment either encourages or restricts older adults from being physically active outdoors (Chaudhury et al., 2016). Living in a neighborhood where it is safe to walk with well-kept streets, good public transport, public facilities, and open public and green spaces has been associated with higher levels of mobility and physical activity (Barnett et al., 2017; Portegijs et al., 2017; Timmermans et al., 2016a; Yun, 2019). Engaging in social activities might also promote physical activity. For example, a cross-sectional study among older Japanese people found that those who participated in social activities were also more physically active (Kikuchi et al., 2017). Luo and colleagues reported similar results in an international comparison of six countries (Luo et al., 2020).

To describe why individuals with conditions limiting their mobility, such as LLOA, are more affected by the neighborhood environment when it comes to social participation and physical activity, we apply the theoretical framework of the Person-Environment (P-E) fit model (Lawton and Nahemow, 1973). The P-E fit suggests that human behavior is influenced by the interaction between individual competence (i.e., functional, biological, cognitive, social, and behavioral skills and abilities) and environmental pressure (Clarke and Nieuwenhuijsen, 2009; Scheidt and Norris-Baker, 2003). The Environmental Docility Hypothesis (Lawton, 1986), which is derived from the P-E fit, suggests the greater an individual's impairment, the more significant the impact of the environment on that individual. Accordingly, reduced physical activity levels might result from environmental barriers and social participation restrictions and will be especially pronounced in older adults with LLOA.

Empirical findings have demonstrated that older adults with osteoarthritis are more dependent on the neighborhood environment because they are more restricted in their daily mobility within the community (Rantakokko and Wilkie, 2017; Rosso et al., 2011). Aspects of neighborhood environment, such as street conditions and traffic, proximity to destinations and green spaces, safety, and public transport have all been identified as more critical for people with osteoarthritis compared to healthy adults (Martin et al., 2012; Timmermans et al., 2017; van der Pas et al., 2016). Moreover, limited access to neighborhood resources restricts individual's social participation over the long-term (Vaughan et al., 2017). Research has indicated that limited availability to a car and public transit results in an increased odds of participation restriction of older adults with knee pain (Wilkie et al., 2007).

Community-dwelling older adults with self-reported osteoarthritis have reported more participation restrictions (Machado et al., 2008). A review identified that social support from family and friends and opportunities to socialize influenced physical activity amongst older adults with osteoarthritis (Kanavaki et al., 2017). Therefore, being unable to participate in social life is a significant concern for older adults with osteoarthritis (Busija et al., 2013; Carr, 1999).

No study has explored the structural relationship between neighborhood resources, social participation, and physical activity simultaneously, within people who have LLOA and who may have particular physical activity challenges due to their disease. Based on the literature, there is reasonable evidence for a single pathway linking physical activity to neighborhood resources (Portegijs et al., 2020) and to social participation (Kanavaki et al., 2017). This is also the case for the linkage between neighborhood resources and social participation (Vaughan et al., 2017). Accordingly, we analyzed the relationship between physical activity with neighborhood resources and social participation. Moreover, we simultaneously assessed the association between neighborhood resources and social participation.

Informed by the P-E fit and previous literature, we derived two hypotheses: (1) older adults with LLOA are more dependent on neighborhood resources for social participation and physical activity compared to people without LLOA, and (2) social participation mediates the association between neighborhood resources and physical activity.

2. Methods

2.1. Sample

Data were gathered from the European Project on Osteoarthritis (EPOSA). EPOSA is a longitudinal observational population-based study which includes data from six European cohort studies (Germany, Italy, the Netherlands, Spain, Sweden, and the United Kingdom) on older community-dwelling persons aged 65–85 years at baseline in all cohorts except for the United Kingdom which has an age range from 71 to 80. A detailed description of the cohorts and the measurements is published elsewhere (van der Pas et al., 2013). Baseline data collection commenced between November 2010 to March 2011 in all six countries and ceased between September 2011 to November 2011. Participants responded to the same questionnaires at a follow-up interview after 12–18 months ($M_{\text{mean time to follow up}}$: 13.8 months; $SD = 2.2$). Informed written consent was obtained from all participants before the interview. EPOSA includes 2942 participants, from which 2455 (83%) agreed to a follow-up evaluation. Participants were excluded from this analysis if they had missing values on clinical LLOA ($n = 28$), previous unilateral or bilateral knee replacement ($n = 54$), more than 50% missing values on the neighborhood resources measures ($n = 18$), or more than 50% missing items on the social participation scales ($n = 69$). The final analytic sample comprised of 2286 (77.7%) participants. Drop-outs were more likely to be older ($M_{\text{drop-out}} = 75.4$ years vs. $M_{\text{included}} = 73.8$ years; $p < .001$), female (drop-out: 57.4% vs. included: 50.3%; $p < .001$), and reported significantly lower physical activity than those that participated at follow-up ($M_{\text{drop-out}} = 57.9$ min/day vs. $M_{\text{included}} = 71.0$ min/day; $p < .001$).

2.2. Measures

Trained study nurses interviewed all participants at home or in a clinical center. The study incorporated a standardized questionnaire and a clinical examination (van der Pas et al., 2013).

2.3. Physical activity

The validated Longitudinal Aging Study Amsterdam Physical Activity Questionnaire (LAPAQ) was used to assess physical activity at baseline (Stel et al., 2004). The LAPAQ measures the frequencies and durations of six activities (walking for transport, cycling, gardening, light household work, heavy household work, and a maximum of two types of exercise) in the last two weeks. Extreme outliers ($>4 SD$) were separately identified for each country and set to the 4th standard deviation value. A total physical activity score was calculated by adding up walking for transport, cycling, and exercise. Physical activity was square-root transformed to meet the normal distribution assumptions in the models.

2.4. Neighborhood environment

The neighborhood resources were assessed at baseline using the four-item modified version of the Home and Community Environment (HACE) instrument (Keysor et al., 2010; White et al., 2010). The HACE is a standardized, self-report instrument designed to assess barriers or facilitators in an individual's environment that may influence their social participation (Keysor et al., 2005). The modified version kept community mobility and transportation items, which have been shown to be essential for older adults with functional limitations. We examined the following four features of the neighborhood resources from the HACE: (1) parks and walking areas that are easy to get to and easy to use; (2) places to sit and rest at bus stops, in parks, or in other places where people walk; (3) public transportation close to home; (4) public facilities (such as a daily supermarket, bus stop, etc.). Response categories were two ('a lot'), one ('some'), and zero ('not at all'). Each of the four items

reflects the presence or absence of an environmental feature. For descriptive purposes, we calculated a total score with a possible range from zero to eight, where higher scores equated to more neighborhood resources. The internal consistency (Cronbach's α) for this scale was 0.80.

2.5. Social participation

The Maastricht Social Participation Profile included nine questions to determine the frequency and diversity of social involvement for older people with chronic diseases (Mars et al., 2009). The following nine items comprised social participation: 'How often in the past four weeks have you (taken part in/been to): (1) a club, interest group or activity group, church or other similar activity; (2) a cultural or educational event such as the cinema, theatre, museum, talk or course; (3) eaten out; (4) out to a pub, café or tearoom; (5) a public event; (6) an organized games afternoon or evening; (7) a day trip organized by a club or society; (8) committee work for a club, society or another group; (9) any organized voluntary work?' The response categories range from zero ('not at all') to three ('more than twice a week'). We calculated total scores for descriptive purposes, ranging from zero to 27 (Cronbach's $\alpha_{\text{baseline}} = 0.64$; $\alpha_{\text{follow-up}} = 0.64$), where higher scores equated to higher social participation.

2.6. Lower limb osteoarthritis

Clinical hip and knee osteoarthritis were diagnosed using the American College of Rheumatology (ACR) criteria (Altman et al., 1986; Zhang et al., 2010). The diagnosis of clinical hip osteoarthritis was based on self-reports and physical examination: pain in the hip was evaluated by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score (cutoff score = 3, range: 0–20), plus all of: pain associated with hip internal rotation in at least one side; morning stiffness lasting <60 min evaluated by the WOMAC stiffness subscale (score from 'mild' to 'extreme'); and over 50 years of age (Bellamy, 2008). The clinical knee osteoarthritis diagnosis required pain in the knee as evaluated by the WOMAC pain subscale score, plus three of the following criteria: age above 50 years; morning stiffness lasting <30 min, evaluated by the WOMAC stiffness subscale; crepitus on active motion in at least one side; bony tenderness in at least one side; bony enlargement in at least one side; and no palpable warmth of synovium in both knees. Joint pain was assessed using the relevant subscale of the WOMAC questionnaire, with a cut point of ≥ 3 as the pain criterion (van der Pas et al., 2013). Having LLOA was defined when clinical hip and/or knee osteoarthritis was present.

2.7. Potential covariates

Several variables were utilized in the models as adjustment covariates: age in years, the average temperature; Body Mass Index (BMI); and self-rated health. The average daily temperature (in degrees Celsius) was recorded for each day and summarized for each participant over the last 14 days before the LAPAQ. Data were extracted from local weather stations within a maximum distance from the participant's residence of 80 km (Timmermans et al., 2016b). BMI was calculated as weight in kilograms divided by height in meters squared. Weight was measured to the nearest 0.1 kg using a calibrated scale. Height was measured to the nearest 0.01 m using a stadiometer. Self-rated health was determined using a five-point Likert-scale response to the following question; "How is your health in general?" Response categories were: five ('very good'), four ('good'), three ('fair'), two ('poor'), and one ('very poor') (Robine et al., 2003).

Data were analyzed using STATA 15.0 software (StataCorp LP, Texas, USA) and AMOS 24 (IBM SPSS, Chicago, USA). The study sample characteristics were presented using means (M) and standard deviations (SD) for continuous variables and frequencies for dichotomous or

categorical variables. First, Pearson's correlation analyses were introduced, followed by Structural Equation Modeling (SEM) testing if social participation mediated the relationship between neighborhood resources and physical activity. All three single pathways and the mediation were also tested if LLOA moderated the associations (see the theoretical model in Fig. 1).

Social participation and neighborhood resources were operationalized as a latent construct. In the final model, we applied a cross-lagged approach to specify the predictive direction between social participation and physical activity. This approach includes information about the stability of the main variables over time and reverse causality (Anderson and Kida, 1982). Positively correlated items of the social participation scale were parceled or aggregated and used as indicators of latent constructs in the SEM (Matsunaga, 2008). We considered an effect to be mediated in the presence of a significant indirect effect (Preacher and Hayes, 2004). We calculated a bootstrapped correlation matrix with a bias-corrected accelerated 95% confidence interval (CI) based on 1000 samples. Missing data ($N = 140$) were imputed to avoid standard error deflation under the assumption that missing data occurred randomly.

Full information maximum likelihood estimation was used to assess the model fit and the following fit indexes were calculated: χ^2 test statistic, the root mean square error of association (RMSEA), the comparative fit index (CFI), and the Tucker–Lewis index (TLI). We conducted a sensitivity analysis comparing the complete case analysis with the imputed dataset analysis.

3. Results

3.1. Demographic characteristics

The characteristics of the sample are summarized in Table 1. At baseline, mean age was 73.8 years ($SD = 5.0$). Combining older adults with clinically diagnosed knee osteoarthritis ($N = 436$) and hip osteoarthritis ($N = 134$), we identified 489 older adults (21.4%) with LLOA. Participants reported that 1.7 ($SD = 1.5$) from a total of four inquired environmental features were very often available in the neighborhood.

When comparing participants with LLOA with older adults without the condition, we found the following baseline differences: they were more often female (65.0% vs. 46.3%; $p < .001$), with lower educational attainment (more than secondary education: 45.0% vs. 61.0%; $p < .001$), reported less social participation ($M_{\text{LLOA}} = 5.2$ vs. $M_{\text{No LLOA}} = 5.8$; $p = .001$), reported worse self-rated health ($M_{\text{LLOA}} = 3.4$ vs. $M_{\text{No LLOA}} = 3.9$; $p < .001$), and were less physically active ($M_{\text{LLOA}} = 56.4$ vs. $M_{\text{No LLOA}} = 74.9$ min per day; $p < .001$) (Table 1).

3.2. Cross-sectional analysis

Bivariate correlation analysis revealed neighborhood resources had

Fig. 1. An analytic model of the structural equation model examining the causal relationship between the neighborhood resources, physical activity, and the indirect effect of social participation. All paths are assumed to be moderated by lower limb osteoarthritis. Error terms are not depicted.

Table 1
Characteristics of the study population, stratified by LLOA (N = 2286).

	Total (N = 2286)		LLOA (N = 489)		No LLOA (N = 1797)		p-value
Age, <i>M</i> (<i>SD</i>) years	73.8	(5.0)	74.2	(5.1)	73.8	(5.0)	.072
Female, %	50.3		65.0		46.3		<.001
Educational level (≥secondary education), %	57.6		45.0		61.0		<.001
Self-rated health ¹ , <i>M</i> (<i>SD</i>)	3.8	(0.8)	3.4	(0.8)	3.9	(0.8)	<.001
Living with a partner, %	68.3		66.3		68.9		.267
Temperature (°Celsius), <i>M</i> (<i>SD</i>)	12.0	(5.4)	11.6	(5.6)	12.0	(5.3)	.115
Neighborhood resources (T1) (count 'at lot') ² , <i>M</i> (<i>SD</i>)	1.7	(1.5)	1.6	(1.5)	1.7	(1.5)	.167
Neighborhood resources (T1) (index) ³ , <i>M</i> (<i>SD</i>)	5.2	(2.1)	5.0	(2.2)	5.3	(2.0)	.030
Social participation (T1) ⁴ , <i>M</i> (<i>SD</i>)	5.7	(3.8)	5.2	(3.8)	5.8	(3.8)	.001
Social participation (T2) ⁴ , <i>M</i> (<i>SD</i>)	5.3	(3.7)	4.9	(3.8)	5.4	(3.6)	.001
Physical activity (minutes/day) (T1) ⁵ , <i>M</i> (<i>SD</i>)	71.0	(69.8)	56.4	(53.4)	74.9	(73.3)	<.001
Physical activity (minutes/day) (T2) ⁵ , <i>M</i> (<i>SD</i>)	64.7	(64.2)	57.5	(59.6)	66.7	(65.2)	.002

Notes. *M* = mean; *SD* = standard deviation; LLOA = lower limb osteoarthritis; T1 = baseline (2010/2011); T2 = 1 year follow-up (2011/2012); ¹ possible range from 1 to 5; ² possible range from 0 to 4; ³ possible range from 0 to 8; ⁴ possible range from 0 to 27; ⁵ raw data are presented.

significant positive relationships with physical activity ($r = 0.19$; $p < .001$) and social participation ($r = 0.10$; $p < .001$). The first hypothesis assumed that individuals with LLOA are more dependent on neighborhood resources than older adults without osteoarthritis. At baseline, correlation analyses confirmed the following significant group differences: neighborhood resources were more highly correlated with physical activity ($r_{\text{LLOA}} = 0.26$; $r_{\text{No LLOA}} = 0.16$; $p = .043$) in older adults with LLOA (Table 2). Correlations between neighborhood resources and social participation were in the same direction ($r_{\text{LLOA}} = 0.13$; $r_{\text{No LLOA}} = 0.08$; $p = .313$) but did not reach significance. Consistent patterns have been found for every single country except for Italy, with higher correlations among persons without LLOA (Supplement 1).

3.3. Evaluation of the measurement and structural models

On initial examination, the measurement model did not yield a good model fit ($\chi^2(38) = 312.7$; CFI = 0.937; TLI = 0.907; RMSEA = 0.056).

Table 2
Correlations between social participation, physical activity, and neighborhood resources.

	1	2	3	4	5
1 Social participation (T1)		.70 ***	.08 ***	.20 ***	.14 ***
2 Social participation (T2)	.72 ***		.06 *	.17 ***	.13 ***
3 Neighborhood resources (T1)	.13 **	.12 **		.16 ***	.17 ***
4 Physical activity (T1)	.16 ***	.13 **	.26 ***		.48 ***
5 Physical activity (T2)	.15 ***	.20 ***	.21 **	.52 ***	

Notes. * $p < .05$, ** $p < .01$, *** $p < .001$; $N = 2286$; T1 = baseline (2010/2011); T2 = 1-year follow-up (2011/2012); Inter-measurement interval = 13.4 months; The lower left section represents persons with lower limb osteoarthritis (LLOA); the upper right section represents persons without LLOA.

The model fit was improved by correlating one error term between two neighborhood resources. This revised baseline measurement model fit the data well ($\chi^2(36) = 121.5$; CFI = 0.980; TLI = 0.970; RMSEA = 0.032). The models were based on imputed data. Sensitivity analyses revealed that the standardized coefficients were almost identical, comparing the imputed and complete case sample of 2146 participants.

3.4. LLOA as moderator of the direct and indirect paths

The first hypothesis expected stronger associations in persons with LLOA in comparison to people without LLOA. Therefore, older adults with LLOA were compared to individuals without LLOA using a multi-group SEM (Fig. 2). Even though the correlations between neighborhood resources and physical activity/social participation indicated stronger associations in those with LLOA, the groups did not differ significantly. Neighborhood resources were directly associated with social participation and physical activity. Following the second hypothesis, neighborhood resources and physical activity were indirectly related because social participation served in both groups as a significant mediator ($\beta_{\text{LLOA}} = 0.046$; $p = .002$; $\beta_{\text{No LLOA}} = 0.020$; $p = .012$). In addition, we tested for a moderated mediation by LLOA status. Even though the LLOA group's mediation was more than twice the numerical size compared to the group of older adults without LLOA, the moderated mediation did not reach significance ($p = .114$).

3.5. Prospective analyses

The cross-sectional SEM model was extended by a cross-lagged longitudinal approach (Fig. 3). At 12–18 months follow-up, people with LLOA were more physically active if they reported more neighborhood resources ($\beta = 0.145$; $p = .002$) and higher social participation ($\beta =$

Fig. 2. Multi-group structural equation model (cross-sectional) examining the causal relationship between the neighborhood resources, physical activity, and the indirect effect of social participation. * $p < .05$, ** $p < .01$, *** $p < .001$; LLOA = Lower limb osteoarthritis; Standardized parameter estimates for pathways are presented; Covariates are omitted in the figure for reasons of parsimony. The models were adjusted for age, self-rated health, body mass index, and temperature; The ellipses represent latent constructs. The rectangles depict observed variables; arrows represent the hypothesized direction of effects. Model fit indices: $\chi^2(118) = 623.4$, CFI = 0.902, TLI = 0.870, RMSEA = 0.043. Calculations are based on the imputed sample ($N = 2286$).

Fig. 3. Multi-group structural equation model (longitudinal) examining the causal relationship between the neighborhood resources, physical activity and the indirect effect of social participation. $\forall < .10$, $*p < .05$, $**p < .01$, $***p < .001$; LLOA = Lower limb osteoarthritis; Standardized parameter estimates for pathways are presented; Covariates are omitted in the figure for reasons of parsimony. The models were adjusted for age, self-rated health, body mass index and temperature; The ellipses represent latent constructs, and the rectangles depict observed variables; arrows represent hypothesized direction of effects. Inter-measurement interval = 13.8 months; Model fit indices: χ^2 (248) = 1171.2, CFI = 0.914, TLI = 0.894, RMSEA = 0.040; Calculations are based on the imputed sample ($N = 2286$).

0.077; $p = .098$) at baseline. Social participation served again as a mediator between neighborhood resources and prospective physical activity in people with LLOA ($\beta = .018$; $p = .013$) but not in older adults without LLOA ($\beta = 0.001$; $p = .864$).

4. Discussion

This study offers new knowledge about social participation as a pathway linking neighborhood resources and physical activity. We applied the conceptual P-E fit using longitudinal data to examine the association between neighborhood resources and physical activity. The results showed that the physical activity of older adults with LLOA is more strongly associated with neighborhood resources compared to people without LLOA. This indicates that older adults with LLOA are more dependent on neighborhood resources. Furthermore, participating in social aspects of life was more important for prospective physical activity in older adults with LLOA than individuals without LLOA.

Neighborhood resources directly affect people's capacity and motivation towards physical activity and alter the ability and opportunity to participate in social activities within a neighborhood, leading to physical activity. Social participation partially mediated the relationship between neighborhood resources and prospective physical activity in people with LLOA, while there was no effect in individuals without the condition. That suggests that social participation is more important for older adults with LLOA to maintain a physically active lifestyle.

Neighborhood resources and physical activity were closely associated, especially in older adults with LLOA. This is in line with previous research that reported more significant mobility restrictions in older adults with osteoarthritis when environmental barriers were present (Rantakokko and Wilkie, 2017). Overall, there is strong evidence of the positive associations between neighborhood resources (i.e., safety, access to parks, accessibility, and public transit), mobility limitations (Eronen et al., 2014), and physical activity in older adults (Barnett et al., 2017; Haselwandter et al., 2015; Moran et al., 2014).

There are differences in how individuals with and without LLOA experience their neighborhood. This study reports a trend in the anticipated direction (derived by the P-E fit model) that older adults with LLOA were more dependent on the neighborhood resources for social participation and physical activity. The observed associations with neighborhood resources were weaker than expected. This discrepancy may be due to the HACE measurement approach, which might not have captured all relevant environmental aspects that hinder physical activity

in people with LLOA (i.e., the slope and condition of sidewalks, safety, and aesthetics of the neighborhood). Future research may incorporate neighborhood resources' availability by using objective data on the neighborhood in combination with Global Positioning System devices. Objective data would allow a more detailed assessment of variables, including terrain and pavement conditions, which may be particularly crucial for older adults with LLOA.

This study also has some caveats. Firstly, as is common in aging studies, a high drop-out rate of 22% biased the results towards a healthier population, compromising the ability to generalize the results. Our analyses were adjusted for individual and outdoor environmental factors. Despite this, we cannot rule out that all relevant factors were accounted for, and some residual effects may remain. However, the EPOSA dataset offered the unique opportunity to test hypotheses drawn from a theoretical P-E fit model using prospective analyses in samples of older adults from six European countries. All single cohorts were recruited from representative population samples. Secondly, the study focused on the outdoor environment and did not account for the home environment, including access to the residence. The entrance, however, might not have constituted a barrier to the participants being physically active because older adults with LLOA who needed to use stairs are marginally but not significantly less physically active than older adults with LLOA who enter the house at street level or with the elevator. A further limitation was that the used physical activity questionnaire asked about a limited number of activities. It may not entirely have captured the activities of everyday life (Durante and Ainsworth, 1996) or, conversely, may overestimate the duration of some daily physical activities because of difficulties accurately recalling daily activities (Herbolzheimer et al., 2018). However, standardized assessments of social participation and a validated physical activity questionnaire were used. Accelerometers may be suitable instruments assessing physical activity in future studies, in addition to the information from questionnaires. Lastly, the follow-up time of one year in this study might limit the ability to identify a change in all constructs. This might be why we only detected small effects in the prospective analyses.

Future research might expand upon this study by examining how older adults, particularly those with LLOA, engage in physical activity. LLOA management might include strategies for maintaining regular physical activity in the neighborhood, considering the relevance of participation in social activities.

5. Conclusion

It is essential to recognize that older adults' physical activity results from the complex inter-relationships between disease symptoms, the neighborhood environment, and options to participate in society. Objective and perceived characteristics of the neighborhood environment in which people live and the opportunity to socially participate might enable people with physical limitations to continue being physically active.

Declaration of competing interest

No competing interests are declared.

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Appendix A. Supplementary data

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