Effect of Change of Interleukin-6 Over Time on Gait Speed Response: Results From the Lifestyle Interventions and Independence for Elders Study

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SUMMARY

Interleukin (IL)-6 is a well-accepted biomarker of chronic low-grade inflammation possibly conditioning the effect of physical activity (PA) intervention on physical performance in mobility-limited older adults. We evaluated PA intervention effects on 400 m gait speed by yearly change of IL-6 levels in a post-hoc analysis from Lifestyle Interventions and Independence for Elders (LIFE) Study, a multicenter single-blind randomized clinical trial on 1,300 sedentary older adults (mean age:78.85±5.23,65.85% women) at risk for mobility disability. We compared the intervention effects on 400 m gait speed at 12 months follow-up, according to yearly IL-6 change categorized for 1 pg/ml increase or decrease, and subsequently for larger range of yearly variation. Among subjects with yearly IL-6 change between -1 and +2 pg/ml, we observed a significant difference of gait speed in PA intervention group compared to healthy educational intervention group [0.041 m/sec,95% confidence interval (CI):0.008 to 0.074,p=0.006;Cohen's d:0.26, 95% CI:0.12 to 0.41). No effects were observed on 400 m gait speed for wider range of variation of plasma IL-6 levels. Limiting change of IL-6 levels under this specific hormetic window could be an important goal to achieve better benefit from PA intervention in terms of gait speed change and prevention of mobility disability.

Keywords: physical activity; interleukin-6; gait speed; older adults; randomized clinical trial

1. INTRODUCTION

Gait speed represents an objective measure of physical functioning, with slower performances associated with mobility disability and other adverse health outcomes in older adults (Abellan van Kan et al., 2009; Studenski et al., 2011). Gait speed lower than 0.8 m/sec is a reliable cut-off to identify subjects at increased risk for disability, hospitalization, institutionalization and death (Cruz-Jentoft et al., 2019), while improvement of usual gait speed may ensure a better life expectancy in older adults (Hardy et al., 2007).

Multicomponent exercise intervention is one of the best and safe approach improving gait speed in older adults (Lopopolo et al., 2006). Results from Lifestyle Interventions and Independence for Elders (LIFE) study showed that over 2.6 years follow-up, multicomponent structured physical activity (PA) intervention led to small, but clinically meaningful, improvement of gait speed over 400 meters (0.05 m/sec) (Miller et al., 2018; Santanasto et al., 2017). Gait speed measured over long distances (400 m) is a good indicator of cardio-respiratory fitness (Simonsick et al., 2006), and it may be a better early indicator of the overall physical health compared to gait speed over short distances (Newman et al., 2006). However, not all the subjects undergoing PA intervention respond in the same way in term of improvement of physical function and cardio-respiratory fitness (Whipple et al., 2018). Therefore, it is important to determine the biological mechanisms by which PA affects 400 m gait speed, to better understand key pathways involved in determining mobility disability.

Chronic low-grade inflammation has been recognized as one of the potential underlying causes of age-related diseases (Franceschi and Campisi, 2014), associated with physical inactivity (Warnberg et al., 2010) and recognized as an independent risk factor for incident disability, impaired mobility, and mortality (Chung et al., 2009). Interleukin (IL)-6 is a well-accepted marker of systemic inflammation in older adults which has been defined as the “cytokine of gerontologists” (Ershler, 1993). IL-6 circulating levels are higher in individuals aged 70 and older and are strongly related to physical disability (Ferrucci et al., 1999). IL-6 is also a myokine, a cytokine secreted by skeletal muscle cells, acting as important regulator of muscle perfusion, fuel distribution and whole-body metabolism during exercise bouts (Reihmane and Dela, 2014).

Evidence on the relationship between circulating IL-6 levels and gait speed suggests that higher IL-6 levels may be associated to poorer performance in older adults (Kositsawat et al., 2020; Newman et al., 2016; Verghese et al., 2011). Findings from the Health ABC study showed that only chronic exposure to high IL-6 levels, rather than the isolated elevation of IL-6 values or its change over time, were associated to slower gait speed in community-dwelling older adults (Nadkarni et al., 2016). To date, the effects that dynamic changes of IL-6 have on gait speed during PA intervention among mobility-limited older adults is not well understood. We hypothesized that different changes in elevation or reduction of plasma IL-6 levels, over 12 months follow-up, may evoke different responses to PA intervention in term of gait speed in the Lifestyle Interventions and Independence for Elders (LIFE) Study.

2. METHODS

2.1. Study design and participants

The LIFE Study is a multicenter, single-blind, parallel randomized trial designed to compare a long-term moderate–intensity PA program with a successful aging intervention detailed elsewhere (Fielding et al., 2011; Pahor et al., 2014). Between February 2010 and December 2013 were enrolled 1,635 sedentary older persons (aged 70 to 89 years) with mobility limitations from eight US centers. Inclusion criteria were: sedentary lifestyle (reporting <20 min/wk in the past month performing regular PA and <125 min/wk of moderate PA at the Community Healthy Activities Model Program for Seniors (CHAMPS-18) questionnaire (Stewart et al., 2001), lower extremity functional limitation as measured by Short Physical Performance Battery (SPPB) score ≤9 (Guralnik et al., 2000) and ability to walk 400 m in less than 15 minutes without sitting, leaning, or the assistance of another person. Subjects were excluded if: nursing home residents, or unable to communicate with study personnel for speech/hearing problems, or having medical conditions, i.e., cognitive impairment as assessed by Modified Mini-Mental State Examination (3MSE) (Teng and Chui, 1987) score 1.5 standard deviations below education- and race-specific norms, arthritis awaiting joint replacement, severe cardiovascular diseases, respiratory disease requiring regular use of corticosteroids or oxygen, active cancer, end-stage renal disease in dialysis, psychiatric disease including alcohol abuse, neurodegenerative disorders including Parkinson's disease, terminal illnesses or other physical complains which not allowed them to safely participate in the intervention. The study protocol was approved by the institutional review boards of all participating sites (clinicaltrials.gov identifier: NCT01072500). For this post-hoc analysis we evaluated 1,300 participants (79.51%) with data on IL-6 assessment both at baseline and after 12-month follow-up (Figure 1).

2.2. Interventions

Details on intervention procedures have been described elsewhere (Fielding et al., 2011; Pahor et al., 2014). Briefly, the PA intervention consisted of two group sessions a week performed at the center associated with home-based activity three to four times a week. The PA sessions focused on: 30 min of

walking at a moderate intensity (at least 150 min/week), 10 min of primarily lower extremity strength training, 10 min of balance training, and 3–5 min of flexibility/stretching exercises. Using the Borg's scale of self-perceived exertion (Borg, 1982), participants were instructed to exercise at "somewhat hard" intensity during walking activity, and at "hard" intensity during strength training. The healthy educational (HE) intervention consisted of workshops on topics of interest for older adults (e.g., travel safety, preventive services and screenings appropriate for different ages, nutritional advice) excluding purposefully PA topic. Sessions were performed weekly in the first 26 weeks and then monthly or bimonthly at the discretion of each subject. At the end of every seminar, participants in the HE intervention performed 5–10 minutes of light, upper extremity stretching.

2.3. Measurements

2.3.1. Interleukin-6

Blood samples were collected from participants in the early morning (between 7 and 9 a.m.) after a 12-hour fast at the baseline and the 12-month assessment visits. To avoid influence of potential confounders, 12-month blood sampling was collected at least 24 hours after the last acute bout of exercise training and postponed (1–2 weeks after recovery of symptoms) in the event of an acute respiratory, urinary tract, or other infection. Samples were collected and stored locally at -80°C until shipment to the Biological Specimen Repository at University of Vermont. Plasma IL-6 was determined using the Quantikine high-sensitivity enzyme-linked immunosorbent assay kit from R&D Systems (Minneapolis, MN). All samples were measured in duplicate, and the average of the two values was considered for the analysis.

2.3.2. 400 meters gait speed

Centrally trained and certified research staff, blinded to randomization assignment, instructed participants to walk 10 laps on a 20 m course at their usual pace (40 m/lap). At each field center, the walk course was located in a dedicated hallway with traffic cones on both ends 20 m apart. Participants can use a cane or rest up to 1 minute, but they cannot sit, lean against the wall, or get the assistance of

another person or walker. If the participant reports chest pain, tightness or pressure, significant shortness of breath or difficulty breathing, or feeling faint, lightheaded or dizzy, the test was stopped marking the point at which he/she stopped and recording the total distance performed. Gait speed was calculated by dividing the meters walked prior to stopping by time walked in seconds.

2.4. Statistical analysis

Baseline characteristics stratified by intervention group were summarized using means and standard deviations or counts and percentages. Spearman's correlation was performed to test the association between change in 400 m gait speed and changes in IL-6 values (ΔIL-6) over 12-month follow-up. We compared the intervention effects on 400 m gait speed based on ΔIL-6 between baseline and follow-up, using separated repeated measures analysis of covariance with an unstructured parameterization matrix for longitudinal covariance. IL-6 values were winsorized to limit the influence of extreme values; this was done by replacing values less than the first percentile of the cohort wide distribution with the value of the first percentile and replacing values greater than the 99th percentile with the 99th percentile value.

ΔIL-6 was categorized according to a 1-unit (pg/ml) change in reduction or increase of IL-6 values as dummy variables (e.g., code "1": for IL-6 reduction between 0 and -0.999 pg/ml and code "0" for the others, and so on for the other ranges). ΔIL-6 was categorized as dummy variables according to a change over time of IL-6 values on a larger range of variation (code "1" for ΔIL-6 between 0 and 1.999 pg/ml or -0.999 and 0.999 pg/ml or -0.999 and 1.999 pg/ml or -1.999 and 1.999 pg/ml or -1.999 and 2.999 pg/ml, and code "0" for the other ΔIL-6 values).

In order to adjust for the differences at baseline between the PA and HE groups, the intervention effect was estimated without the intervention variable in the statistical models:

$$Y_{it} = \beta_0 + \beta_{1\ \text{time}} + \beta_{2\ \Delta\text{IL-6}} + \beta_{3\ \text{Intervention} \times \text{time}} + \beta_{4\ \text{Intervention} \times \Delta\text{IL-6}} + \varepsilon_{it}$$

where Y_{it} are the observations for subject *i* at time *t*, β_1 is the regression coefficient for time of measurement (0 for the baseline measurement and 1 for the follow-up), β_2 is the regression coefficient for the ΔIL-6, β_3 is the regression coefficient for the interaction between the intervention variable and

time, β_4 is the regression coefficient for the intervention variable and ΔIL-6, and ε_{it} is the "error" of individual *i* at time *t*. Because the intervention variable was not in the model, the baseline values for both PA and HE intervention groups were assumed to be equal and are reflected in the intercept of the model (i.e., β_0). This strategy corresponds to an analysis of response profiles where the PA and HE group means are constrained to be equal. In a randomized clinical trial (RCT), the baseline value of the outcome is highly related to the outcome at the follow-up measurements, and therefore even a small difference in the baseline value of the outcome between the two intervention groups can have a (strong) confounding effect. It is therefore advised always to adjust for the baseline value of the outcome variable irrespective whether the difference is significant or not (Fitzmaurice et al., 2011). In this model, the coefficient of interest is the regression coefficient for the interaction between the intervention variable and ΔIL-6 (β_4) because this coefficient reflects the intervention effect due to ΔIL-6. All statistical models were adjusted for type 2 diabetes mellitus, hypertension, myocardial infarction, field center, and gender. Contrasts were used to estimate the average effects over time when the $\beta_{4\ \text{Intervention} \times \Delta\text{IL-6}}$ interaction was $p<0.05$. The effect size based on mean comparison was calculated by Cohen's d test for unequal variances (Welch's approximation). We also repeated these analyses among the lowest functioning participants with baseline SPPB scores <9. The p-value for each contrast estimate and its 95% confidence interval (CI) was adjusted by Bonferroni method. The p-value was set at 0.05. All statistical analyses were performed using STATA 16 statistical software (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

3. RESULTS

At baseline, intervention groups were similar in terms of socio-demographic and physical characteristics, cognitive performance, and plasma IL-6 levels (Table 1). PA intervention did not significantly modify plasma concentrations of log-transformed IL-6 compared to HE intervention over 12-month follow-up (p=0.491). However, we found that 400 m gait speed difference between baseline and follow-up was significantly and inversely correlated with ΔIL-6 (ρ= -0.060, p=0.033). Median winsorized ΔIL-6 value between baseline and follow-up in reduction and in increase were respectively -1.092 pg/ml [interquartile range (IQR): -0.476 to -0.368] and 0.924 pg/ml (IQR: 0.405 to 2.119). No significant change of gait speed between intervention groups was found for 1-unit (pg/ml) increase or decrease of IL-6 over time (Table 2).

Since sample size in these small ΔIL-6 intervals was around 20% or less, we performed an exploratory analysis on larger cut-offs which could ensure more balanced distribution in ΔIL-6 categories (Table 2). Among 493 subjects (37.92%) with ΔIL-6 values ranging between 0 and 1.999 pg/ml there was a significant difference of gait speed per year [mean difference (MD): 0.028 m/sec, 95% CI: 0.0003 to 0.057, p=0.047]. Such difference in favor of PA intervention respect to HE intervention was significant both in comparison to subjects with ΔIL-6 range of interest (MD: 0.048 m/sec, 95% CI: 0.008 to 0.088, p<0.010; Cohen's d: 0.27, 95% CI: 0.097 to 0.45), as well as to subjects outside the ΔIL-6 range of interest (MD: 0.019 m/sec, 95% CI: 0.002 to 0.036, p<0.018), and the comparison between the mean difference coefficients of these two groups estimated a significantly faster gait speed performances in subjects with ΔIL-6 range of interest than outside the ΔIL-6 range of interest (MD: 0.028 m/sec, 95% CI: 0.0003 to 0.057, p<0.047). Finally, we estimated a faster gait speed per year within the PA intervention group between subjects with ΔIL-6 values ranging between 0 and 1.999 pg/ml in comparison with subjects with all the others ΔIL-6 values (MD: 0.037 m/sec, 95% CI: 0.007 to 0.067, p<0.008).

Among 780 subjects (60.00%) with a yearly ΔIL-6 values from -0.999 to 1.999 pg/ml, there was a significant difference of gait speed per year (MD: 0.023, 95% CI: 0.0001 to 0.045 m/sec, p=0.05). In particular, subjects with ΔIL-6 values between -0.999 and 1.999 pg/ml in PA intervention respect to HE

intervention group reported a significantly faster gait speed both in comparison to subjects within ΔIL-6 range of interest (MD: 0.041 m/sec, 95% CI: 0.008 to 0.074, p=0.006; Cohen's d: 0.26, 95% CI: 0.12 to 0.41) as well as to subjects outside the ΔIL-6 range of interest (MD: 0.019 m/sec, 95% CI: 0.006 to 0.031, p<0.025). Moreover, the comparison between the mean difference coefficients of these two groups estimated a significantly faster gait speed performances in subjects with ΔIL-6 range of interest than outside the ΔIL-6 range of interest (MD: 0.023 m/sec, 95% CI: 0.0001 to 0.045, p<0.05). Finally, we estimated a faster gait speed per year between subjects with ΔIL-6 values ranging between -0.999 and 1.999 pg/ml in comparison with subjects with all the other ΔIL-6 values (MD: 0.046 m/sec, 95% CI: 0.018 to 0.074, p<0.001). No intervention effect was observed on 400 m gait speed for other yearly variations of plasma IL-6 levels (i.e., from -0.999 to 0.999 pg/ml, from -1.999 to 1.999 pg/ml, and from -1.999 to 2.999 pg/ml). The change over time of plasma IL-6 levels more than 5 pg/mL in elevation or reduction involved less than 10% (129) of participants, then any estimation was not performed.

3.1. Sensitivity analysis on lower functioning participants

Table 3 showed intervention effects on 400 m gait speed by change of IL-6 values in lower functioning participants (SPPB score ≤8). Subjects with yearly reduction of IL-6 values between -1 and -1.999 pg/ml reported a significant difference of gait speed per year (MD: -0.092 m/sec, 95% CI: -0.17 to -0.011, p=0.026). However, no significant difference of gait speed was found between PA intervention and HE intervention groups in this ΔIL-6 range of interest (MD: -0.051 m/sec, 95% CI: -1.21 to 0.225, p=0.430) and within PA intervention group between this ΔIL-6 category compared to other ΔIL-6 values (MD: -0.026 m/sec, 95% CI: -0.93 to 0.35, p=0.353). No significant change of gait speed between intervention groups was found for other considered ΔIL-6.

4. DISCUSSION

The present study demonstrated that 12-month structured, moderate-intensity PA intervention compared to a HE intervention was associated with a significant benefit on 400 m gait speed in mobility-limited older adults in whom plasma IL-6 levels underwent to a yearly change between -1 and +2 pg/ml. The effect size is greater than 0.2, then it should not be considered negligible. In lower functioning participants (SPPB < 8), yearly reduction of IL-6 levels from -1 to -2 pg/ml might lead to greater loss of gait speed performance, but no significant difference was estimated between PA and HE interventions.

The effects of regular exercise training on inflammatory markers are still controversial (Beavers et al., 2010). In the present study, we found that PA intervention did not significantly modify plasma IL-6 levels compared to HE intervention after 12 months follow-up. Less is known about contribution of IL-6 levels on physical performance during PA intervention. Mainstream thinking is that isolated higher IL-6 levels may predict adverse outcomes in older adults (Cesari et al., 2012; Ferrucci et al., 1999). However, the chronic elevation above normal range, as suggested by the definition of inflammaging, may contribute on incidence of adverse health-related outcomes during aging and deterioration of physical functioning (Franceschi and Campisi, 2014; Maggio et al., 2006). Furthermore, in the Health ABC study, repeated measures of serum IL-6, that on average were 2.7 pg/ml over 10-year follow-up, better predicted worsening of gait speed rather than single values of IL-6 or their change (Nadkarni et al., 2016).

For the first time, we reported that a IL-6 change confined between -1 and +2 pg/ml over one year follow-up, in association with moderate-intensity exercise training program, might produce a significantly greater gait speed over long distances (between 0.042 and 0.048 m/sec), both compared to subjects in PA intervention group with other ΔIL-6, and those in the control group with the same yearly ΔIL-6. According to previous evidence, this gait speed difference might be also clinically significant in term of prevention of mobility disability (Miller et al., 2018; Perera et al., 2006). Indeed, changes in gait speed of 0.04-0.06 m/sec have been associated with clinically meaningful modifications in functional limitation (Miller et al., 2018). In contrast with our results, in a small RCT carried out on 99 mobility-limited older adults, Grosicki and colleagues found that change in IL-6 was inversely related with 400 m

gait speed (Grosicki et al., 2020). However, this study examined the effects of 6-month aerobic and resistance training with or without nutrient supplementation on physical performance, therefore it did not have a comparison group for PA intervention and part of the included participants received also a supplementation with proteins and vitamin D which could have altered final IL-6 levels (Grosicki et al., 2020).

Present findings may suggest the presence of an hormetic window for inflammatory state variations, marked by ΔIL-6 levels, which might warrant better responses to PA intervention in terms of gait speed. Traditionally, aging has been considered a consequence of progressive decline in homeostatic capacities (Hayflick, 1998). Therefore, inflammation which is physiologically a protective response of human body to cope with endogenous and environmental stressors including exercise (Franceschi and Campisi, 2014), may reflect a detrimental process when becomes dysregulated in amplitude and duration, as during aging (Franceschi and Campisi, 2014). Inflammation might represent a type of hormetic response also to exercise, in which repeated, transient and mild-intensity stressors may generate beneficial effects (Ji et al., 2016; Santoro et al., 2020). IL-6 is also one of the first identified myokines, and emerged as one of the main signaling molecule released during aerobic exercise, such that it has been recognized as a muscle-derived exerkine (Piccirillo, 2019). IL-6 circulating levels during aerobic exercise increase progressively, peak at the end of the session and then slowly decrease remaining elevated until 6 hours post-exercise session (Ostrowski et al., 1998). IL-6 cascade induced by aerobic exercise might be markedly different form that induced by infections. For example, exercise-induced IL-6 elevation reduced production of another important pro-inflammatory biomarker, the tumor necrosis factor (TNF)-α in response to endotoxin infusion, a stimulus which mimics low-grade inflammation (Starkie et al., 2003). Therefore, in older adults with preserved adaptation capacity, exercise-induced IL-6 response may be an important mechanism silencing inflammatory pathways activated during age-related disease, allowing better benefits on functional performance and potentially slowing down aging process. However, this hypothesis should be verified in *ad hoc* studies with repeated measures of inflammatory markers and longer follow-up.

We found also that lower functioning older adults (SPPB ≤8) experienced a significant worsening of gait speed (-0.082 m/sec) after 12 months when the levels of IL-6 reduced between -1 and -2 pg/ml, but no significant difference was found between subjects assigned to the PA intervention compared to those in the HE intervention arm. Previous data from LIFE Study showed that subjects with SPPB at baseline lower than 9 had more pronounced positive effects of PA intervention *vs.* HE intervention on 400 m gait speed (Santanasto et al., 2017), but this benefit seems not be associated with IL-6 changes. We supposed that frailer subjects with loss of homeostatic capacities leading to excessive reduction of IL-6 levels (likely related to anti-inflammatory drugs use, immunosuppression) might experience greater and faster worsening of functional performances, but further evidence are needed to confirm this hypothesis.

The present study has important strengths including a large sample of mobility-limited older adults, extended intervention and follow-up periods, and high retention rate. However some limitations should be disclosed. First, we analyzed gait speed change only until 12 months follow-up, because IL-6 levels were only measured at baseline and 12-month. Moreover, we do not have information on eventual fluctuations of IL-6 levels during the follow-up, potentially related to acute stressor events, bouts of PA, or medications use, but finally we get information on individual homeostatic capacities in terms of maintenance of stable IL-6 levels. Furthermore, IL-6 was the only available cytokine, therefore future studies should test a broader spectrum of inflammatory biomarkers. Effect on other performances (e.g., muscle strength) and direct measures of cardio-respiratory fitness (e.g., VO2 max) should be further tested. Due to the post-hoc nature of the present study, adjustment for other potential confounders not originally collected (e.g., presence of autoimmune disorders) was not possible. Also the analysis in some ΔIL-6 range might result underpowered for limited sample size. Finally, our results are mainly generalizable to community-dwelling, mobility-limited older adults.

5. CONCLUSION

In conclusion, compared with HE intervention, a moderate intensity, structured PA intervention consisting of walking, lower extremity resistance training and balance regimens produced a small but

clinically meaningful benefit on 400 m gait speed in mobility-limited older adults, when associated with variations of IL-6 between -1 and +2 pg/ml. Further studies are needed to confirm these findings and to test specifically if slight changes of circulating IL-6 during exercise can explain beneficial effects of exercise on other physical performances, body composition, adiposity, glycemic control, cardiovascular and respiratory functions among others.

Statements and Declarations

Competing Interests: No conflicts of interest to declare.

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459 **Table 1** Baseline characteristics of study participants by intervention groups. The Lifestyle

460 Interventions and Independence for Elders (LIFE) Study.

461

Characteristic	Healthy educational intervention (n=652)	Physical activity intervention (n=648)
Age, mean (SD), y	79.143 ± 5.279	78.559 ± 5.173
Sub-Age (>80), n (%)	291/652 (44.63)	264/648 (40.74)
Ethnicity/race (No white), n (%)	117/651 (17.97)	142/646 (21.98)
Women, n (%)	439/652 (67.33)	422/648 (65.12)
Educational, mean (SD), y	3.903 ± 0.826	3.847 ± 0.820
Living alone, n (%)	324/650 (49.85)	289/647 (44.67)
BMI, mean (SD), kg/m^2	30.307 ± 6.082	30.230 ± 5.731
Myocardial infarction, n (%)	54/651 (8.29)	44/646 (6.81)
Hypertension, n (%)	467/651 (71.74)	461/646 (71.36)
Type 2 diabetes mellitus, n (%)	169/651 (25.96)	163/646 (25.23)
Stroke, n (%)	40/651 (6.14)	50/646 (7.74)
Cancer, n (%)	145/651 (22.27)	135/645 (20.93)
Congestive heart failure, n (%)	35/651 (5.38)	18/646 (2.79)
CESD, mean (SD), score	8.791 ± 7.974	8.189 ± 7.479
3MSE, mean (SD), score	91.822 ± 5.277	91.691 ± 5.467
Total cholesterol, mean (SD), mg/dl	178.559 ± 40.198	178.657 ± 38.866
HDL cholesterol, mean (SD), mg/dl	60.672 ± 17.038	60.596 ± 17.871
LDL cholesterol, mean (SD), mg/dl	93.428 ± 33.409	93.105 ± 31.447
Triglycerides, mean (SD), mg/dl	122.588 ± 57.376	125.176 ± 57.116
IL-6, mean (SD), pg/ml	5.146 ± 9.439	5.119 ± 9.990
SPPB, mean (SD), score	7.345 ± 1.605	7.440 ± 1.590
SPPB score<8, n (%)	295/652 (45.25)	281/648 (43.36)
Walk time, mean (SD), m	506.277 ± 110.683	502.108 ± 110.770
400m gait speed, mean (SD), m/s	0.825 ± 0.164	0.831 ± 0.163

4m gait speed, mean (SD), m/s	0.767 ± 0.161	0.770 ± 0.162
Hand grip, mean (SD), kg	24.603 ± 9.573	25.031 ± 9.856

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463 3MSE = Modified Mini-Mental State Examination; BMI = body mass index; CESD = Center for
464 Epidemiologic Studies Depression; HDL = high-density lipoprotein; IL-6 = Interleukin-6; LDL = low-
465 density lipoprotein; SD = standard deviation; SPPB = Short Physical Performance Battery

Table 2 Twelve-month intervention effects on 400 meters gait speed within yearly change of plasma interleukin (IL)-6 levels. The Lifestyle Interventions and Independence for Elders (LIFE) Study.

		Physical activity intervention *vs.* Healthy educational intervention		
IL-6 CATEGORIES (pg/ml) between T0 e T1	**N (%) of involved subjects in yearly ΔIL-6**	**COEFFICIENT**	**95% CI [#]**	**P**
0 to -0.999				
ΔIL-6	287 (22.08)	0.013	-0.015 to 0.042	0.349
time		-0.022	-0.031 to -0.013	<0.001
time x intervention		0.021	0.008 to 0.034	<0.001
ΔIL-6 x intervention		0.010	-0.027 to 0.048	0.584
-1 to -1.999				
ΔIL-6	140 (10.77)	0.005	-0.035 to 0.046	0.798
time		-0.023	-0.032 to -0.014	<0.001
time x intervention		0.022	0.010 to 0.035	<0.001
ΔIL-6 x intervention		-0.034	-0.089 to 0.020	0.220
-2 to -2.999				
ΔIL-6	81 (6.23)	-0.043	-0.087 to 0.002	0.059
time		-0.022	-0.031 to -0.013	<0.001
time x intervention		0.021	0.009 to 0.034	<0.001
ΔIL-6 x intervention		0.008	-0.055 to 0.070	0.803
-3 to -3.999				
ΔIL-6	34 (2.62)	-0.151	-0.229 to -0.073	0.000
time		-0.022	0.031 to -0.013	<0.001
time x intervention		0.021	0.008 to 0.034	<0.001
ΔIL-6 x intervention		0.080	-0.027 to 0.186	0.145
-4 to -4.999				
ΔIL-6	21 (1.62)	-0.001	-0.100 to 0.099	0.989
time		-0.022	-0.031 to -0.013	<0.001
time x intervention		0.022	0.009 to 0.034	<0.001
ΔIL-6 x intervention		-0.054	-0.191 to 0.090	0.586
0 to 0.999				
ΔIL-6	350 (26.92)	0.012	-0.014 to 0.039	0.359
time		-0.022	-0.031 to -0.013	<0.001
time x intervention		0.020	0.007 to 0.033	0.002
ΔIL-6 x intervention		0.022	-0.011 to 0.056	0.188
1 to 1.999				
ΔIL-6	143 (11.00)	-0.015	-0.052 to 0.023	0.438
time		-0.022	-0.031 to -0.013	<0.001
time x intervention		0.020	0.008 to 0.033	<0.001
ΔIL-6 x intervention		0.042	-0.010 to 0.095	0.117
2 to 2.999				
ΔIL-6	74 (5.69)	0.029	-0.036 to 0.095	0.379
time		-0.023	-0.032 to -0.014	<0.001
time x intervention		0.022	0.010 to 0.035	<0.001
ΔIL-6 x intervention		-0.069	-0.155 to 0.017	0.115
3 to 3.999				
ΔIL-6	35 (2.69)	-0.032	-0.117 to 0.052	0.453
time		-0.022	-0.031 to -0.013	<0.001
time x intervention		0.021	0.009 to 0.034	<0.001
ΔIL-6 x intervention		0.027	-0.074 to 0.129	0.598
4 to 4.999				
ΔIL-6	12 (0.92)	0.106	-0.023 to 0.235	0.109
time		-0.023	-0.032 to -0.014	<0.001
time x intervention		0.022	0.009 to 0.035	<0.001
ΔIL-6 x intervention		-0.187	-0.385 to 0.012	0.066

0 to 1.999				
ΔIL-6		0.008	-0.015 to 0.032	0.497
time		-0.021	-0.030 to -0.012	0.000
time x intervention		0.019	0.007 to 0.032	0.003
ΔIL-6 x intervention	493 (37.92)	0.028	0.0003 to 0.057	0.047
(1) vs (2) *		0.048	0.008 to 0.088	0.010¶
(3) vs (4) †		0.037	0.007 to 0.067	0.008¶
(5) vs (6) ‡		0.019	0.002 to 0.036	0.018¶
(7) vs (8) §		0.028	0.0003 to 0.057	0.047¶
-0.999 to 0.999				
ΔIL-6		0.023	0.001 to 0.045	0.043
time	637 (49.00)	-0.021	-0.030 to -0.012	<0.001
time x intervention		0.020	0.007 to 0.032	0.002
ΔIL-6 x intervention		0.017	-0.008 to 0.042	0.173
-0.999 to 1.999				
ΔIL-6		0.024	0.002 to 0.045	0.030
time		-0.021	-0.030 to -0.012	<0.001
time x intervention		0.019	0.006 to 0.031	0.004
ΔIL-6 x intervention	780 (60.00)	0.023	0.0001 to 0.045	0.05
(1) vs (2) *		0.041	0.008 to 0.074	0.006¶
(3) vs (4) †		0.046	0.018 to 0.074	<0.001¶
(5) vs (6) ‡		0.019	0.001 to 0.036	0.025¶
(7) vs (8) §		0.023	0.0001 to 0.045	0.05¶
-1.999 to 1.999				
ΔIL-6		0.028	0.006 to 0.050	0.013
time	920 (70.77)	-0.021	-0.030 to -0.012	<0.001
time x intervention		0.019	0.007 to 0.032	0.003
ΔIL-6 x intervention		0.014	-0.007 to 0.034	0.194
-1.999 to 2.999				
ΔIL-6		0.034	0.012 to 0.057	0.003
time	994 (76.46)	-0.022	-0.031 to -0.013	<0.001
time x intervention		0.020	0.008 to 0.033	0.002
ΔIL-6 x intervention		0.007	-0.013 to 0.027	0.496

ΔIL-6 = follow-up value − baseline value of IL-6; CI = confidence interval

* (1) = ΔIL-6 range of interest values in PA group; (2) = ΔIL-6 range of interest values in HE group

† (3) = ΔIL-6 range of interest values in PA group; (4) = ΔIL-6 other values in PA group

‡ (5) = ΔIL-6 other values in PA group; (6) = ΔIL-6 other values in HE group

§ (7) = ΔIL-6 range of interest values in PA group/ΔIL-6 range of interest values in HE group; (8) = ΔIL-6 other values in PA group/ΔIL-6 other values in HE group

¶ The p-value for each contrast estimate was adjusted using Bonferroni method

All statistical models were adjusted for type 2 diabetes mellitus, hypertension, myocardial infarction, field center, and gender

Table 3 Twelve-month intervention effects on 400 meters gait speed within yearly change of plasma interleukin (IL)-6 among lower functioning participants with baseline Short Physical Performance Battery (SPPB) scores <9. The Lifestyle Interventions and Independence for Elders (LIFE) Study.

		Physical activity intervention *vs.* Healthy educational intervention		
	IL-6 CATEGORIES (pg/ml) between T0 e T1	**COEFFICIENT**	**95% CI**	**P**
400 m WALKING SPEED (m/s)	**0 to -0.999**			
	ΔIL-6	0.007	-0.033 to 0.051	0.722
	time	-0.035	-0.050 to-0.020	<0.001
	time x intervention	0.038	0.018 to 0.058	<0.001
	ΔIL-6 x intervention	0.005	-0.049 to 0.060	0.847
	-1 to -1.999			
	ΔIL-6	0.066	0.004 to 0.129	0.038
	time	-0.036	-0.051 to -0.022	<0.001
	time x intervention	0.041	0.021 to 0.061	<0.001
	ΔIL-6 x intervention	-0.092	-0.174 to -0.011	0.026
	(1) vs (2) *	-0.051	-0.134 to 0.032	0.225
	(3) vs (4) †	-0.026	-0.082 to 0.029	0.353
	-2 to -2.999			
	ΔIL-6	-0.022	-0.081 to 0.038	0.475
	time	-0.035	-0.050 to -0.020	<0.001
	time x intervention	0.038	0.018 to 0.058	<0.001
	ΔIL-6 x intervention	0.024	-0.067 to 0.115	0.600
	-3 to -3.999			
	ΔIL-6	-0.139	-0.223 to -0.056	<0.001
	time	-0.035	-0.049 to -0.020	<0.001
	time x intervention	0.038	0.018 to 0.058	<0.001
	ΔIL-6 x intervention	0.007	-0.099 to 0.113	0.900
	-4 to -4.999			
	ΔIL-6	0.053	-0.061 to 0.168	0.359
	time	-0.035	-0.050 to -0.021	<0.001
	time x intervention	0.039	0.019 to 0.059	<0.001
	ΔIL-6 x intervention	-0.041	-0.205 to 0.122	0.619
	0 to 0.999			
	ΔIL-6	0.012	-0.029 to 0.052	0.574
	time	-0.034	-0.049 to -0.020	<0.001
	time x intervention	0.037	0.017 to 0.057	<0.001
	ΔIL-6 x intervention	0.023	-0.031 to 0.076	0.404
	1 to 1.999			
	ΔIL-6	0.010	-0.042 to 0.063	0.692
	time	-0.036	-0.050 to -0.021	0.000
	time x intervention	0.039	0.019 to 0.059	0.001
	ΔIL-6 x intervention	-0.038	-0.115 to 0.039	0.331
	2 to 2.999			
	ΔIL-6	-0.047	-0.130 to 0.035	0.262
	time	-0.036	-0.050 to -0.021	<0.001
	time x intervention	0.039	0.019 to 0.059	<0.001
	ΔIL-6 x intervention	-0.027	-0.136 to 0.082	0.629
	3 to 3.999			
	ΔIL-6	-0.029	-0.143 to 0.085	0.619
	time	-0.035	-0.050 to -0.020	<0.001
	time x intervention	0.038	0.018 to 0.058	<0.001
	ΔIL-6 x intervention	0.032	-0.100 to 0.163	0.638
	4 to 4.999			
	ΔIL-6	0.124	-0.062 to 0.311	0.191

	time	-0.035	-0.050 to -0.021	<0.001
	time x intervention	0.039	0.019 to 0.059	<0.001
	ΔIL-6 x intervention	-0.208	-0.444 to 0.028	0.084
	0.999 to 1.999			
	ΔIL-6	0.013	-0.021 to 0.047	0.453
	time	-0.035	-0.050 to -0.020	<0.001
	time x intervention	0.038	0.018 to 0.058	<0.001
	ΔIL-6 x intervention	0.004	-0.039 to 0.048	0.837
	-0.999 to 0.999			
	ΔIL-6	0.016	-0.016 to 0.049	0.315
	time	-0.034	-0.049 to -0.020	<0.001
	time x intervention	0.037	0.016 to 0.057	<0.001
	ΔIL-6 x intervention	0.014	-0.024 to 0.053	0.457
	-0.999 to 1.999			
	ΔIL-6	0.019	-0.012 to 0.050	0.234
	time	-0.035	-0.050 to -0.020	<0.001
	time x intervention	0.038	0.018 to 0.058	<0.001
	ΔIL-6 x intervention	0.005	-0.029 to 0.039	0.777
	-1.999 to 1.999			
	ΔIL-6	0.040	0.009 to 0.071	0.012
	time	-0.036	-0.051 to -0.022	<0.001
	time x intervention	0.041	0.021 to 0.061	<0.001
	ΔIL-6 x intervention	-0.012	-0.043 to 0.019	0.440
	-1.999 to 2.999			
	ΔIL-6	0.030	-0.002 to 0.062	0.065
	time	-0.037	-0.051 to -0.022	<0.001
	time x intervention	0.041	0.021 to 0.061	<0.001
	ΔIL-6 x intervention	-0.017	-0.047 to 0.013	0.273

ΔIL-6 = follow-up value − baseline value of IL-6; CI = confidence interval

* (1) = ΔIL-6 range of interest values in PA group; (2) = ΔIL-6 range of interest values in HE group

† (3) = ΔIL-6 range of interest values in PA group; (4) = ΔIL-6 other values in PA group

All statistical models were adjusted for type 2 diabetes mellitus, hypertension, myocardial infarction, field center, and gender

FIGURE LEGEND

Figure 1. Flow of participants through the trial.