Impact and Lessons From the Lifestyle Interventions and Independence for Elders (LIFE) Clinical Trials of Physical Activity to Prevent Mobility Disability

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See related editorial by LaCroix et al. in this issue.

BACKGROUND: Walking independently is basic to human functioning. The Lifestyle Interventions and Independence for Elders (LIFE) studies were developed to assess whether initiating physical activity could prevent major mobility disability (MMD) in sedentary older adults.

METHODS: We review the development and selected findings of the LIFE studies from 2000 through 2019, including the planning phase, the LIFE-Pilot Study, and the LIFE Study.

RESULTS: The planning phase and the LIFE-Pilot provided key information for the successful implementation of the LIFE Study. The LIFE Study, involving 1635 participants randomized at eight sites throughout the United States, showed that compared with health education, the physical activity program reduced the risk of the primary outcome of MMD (inability to walk 400 m: hazard ratio = 0.82; 95% confidence interval = 0.69-0.98; P = .03), and that the intervention was cost-effective. There were no significant effects on cognitive outcomes, cardiovascular events, or serious fall injuries. In addition, the LIFE studies provided relevant findings on a broad range of other outcomes, including health, frailty, behavioral outcomes, biomarkers, and imaging. To date, the LIFE studies have generated a legacy of 109 peer-reviewed publications, 19 ancillary studies, and 38 independently funded grants and clinical trials, and advanced the development of 59 early career scientists. Data and biological samples of the LIFE Study are now publicly available from a repository sponsored by the National Institute on Aging (https://agingresearchbiobank.nia.nih.gov).

CONCLUSIONS: The LIFE studies generated a wealth of important scientific findings and accelerated research in geriatrics and gerontology, benefiting the research community, trainees, clinicians, policy makers, and the general public. **J Am Geriatr Soc 68:872-881, 2020.**

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Walking independently is basic to human functioning. Those who are unable to walk without help are at higher risk of acute and chronic health conditions,

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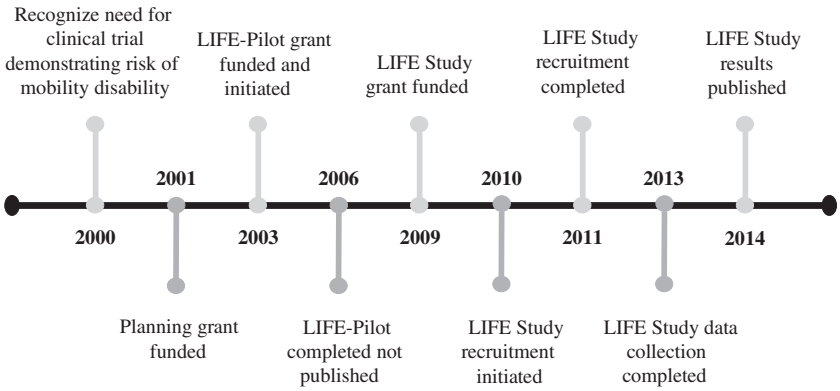

Figure 1. Study time line. LIFE indicates Lifestyle Interventions and Independence for Elders.

disability, hospital admission, institutionalization, and mortality.[1,2] Being able to walk a quarter of a mile, or 400 m, is of pivotal importance for preserving an independent and a high quality of life.[3,4] Epidemiologic studies and smaller clinical trials have shown that engaging in physical activity is associated with several health and functional benefits. However, at the time the Lifestyle Interventions and Independence for Elders (LIFE) Study was planned, it was uncertain whether initiating regular physical activity might avert the risk of major mobility disability (MMD; inability to walk 400 m).

DEVELOPMENT OF THE LIFE STUDIES

The LIFE studies started in year 2000 based on the recognition that there was no conclusive evidence from clinical trials demonstrating that the risk of mobility disability, a major problem for older persons, could be reduced (Figure 1). In 2001, the team received a grant (R21AG19353) to plan a definitive trial with intensive preliminary work involving expert discussions, planning meetings, secondary data analyses of existing cohort studies, and pilot studies,[5] including a study that demonstrated the feasibility of recruiting the target population.[6]

At the end of the planning phase, structured regular physical activity was the most promising intervention to reduce the risk of mobility disability and a pilot study was needed to refine key aspects to ensure the full success of a main larger clinical trial. In the LIFE-Pilot Study, a total of 424 sedentary older persons who were at risk for disability were randomized at four clinical sites to a structured moderate-intensity physical activity intervention compared with a health education intervention and were followed for 1 to 1.5 years (average = 1.2 years) (U01AG022376, 2003-2009).[7] After its conclusion, the LIFE-Pilot Study[8] provided key information and resources for planning the LIFE Study, including the following:

- Demonstrated that the primary outcome of MMD, defined as inability to walk 400 m at usual pace, was valid[8] and statistically efficient[9];
- Developed the primary outcome adjudication procedures for participants not able to come to the clinic;
- Refined the target population who is at risk of MMD;
- Estimated the incidence of MMD in the health education control group to estimate the sample size for the LIFE Study[8];
- Showed that older persons who are sedentary, have impaired physical function, and are at high risk of disability can be successfully recruited, can be retained, and will adhere to a structured physical activity program[10];
- Developed a successful physical activity intervention and a medical safety protocol to reinitiate activity after illness events[8];
- Demonstrated the acceptability and feasibility of the attention control group through a "Successful Aging" health education program;
- Established the internal validity of the intervention by demonstrating its benefits on statistically significant and clinically meaningful improvements of the Short Physical Performance Battery (SPPB) and the 400-m walking speed, which were both prespecified outcomes (Table 1)[8,11]; and
- Established the multicenter structure and quality control procedures for LIFE.

Based on the successes achieved with the LIFE-Pilot, the LIFE Study, which was investigator initiated, was funded in September 2009 (U01AG022376; Figure 1). The LIFE Study was a phase 3 randomized clinical trial to determine whether a structured moderate-intensity physical activity program is more effective than health education in preventing the onset of MMD, defined as inability to walk 400 m. Secondary outcomes included cognitive function; serious fall injuries; persistent MMD; the combined outcome of MMD or death; and cost-effectiveness. Tertiary outcomes included the combined outcome of mild cognitive impairment or dementia, a composite measure of the cognitive assessment battery, physical performance within prespecified subgroups, and cardiovascular events.

Recruitment began in February 2010 and ended in December 2011, 2 months ahead of schedule. Study participants were recruited from urban, suburban, and rural areas at eight clinical centers in the United States. Participants were sedentary men and women, aged 70 to 89 years, who had an SPPB score of less than 10, but were able to walk 400 m. We randomized 1635 participants, who were followed through December 2013, for an average of 2.6 years (range = 2-4 years).[12] As in the pilot study,[7] the two LIFE Study

Table 1. Selected Study Outcomes Measured With Continuous Variables

Outcomes	Unit	Baseline	Follow-Up Time Point, mo	PA	HE	*P* Value
400-m walk self-efficacy	Score	73.3	6	77.8	67.6	<.001
400-m walk self-efficacy	Score	73.3	12	73.5	67.2	.005
Satisfaction with physical functioning	Score	0.3	6	1.1	0.6	.001
Satisfaction with physical functioning	Score	0.3	12	0.9	0.6	.006
Sedentary time	Min	647	6	630	639	<.001
IL-6 biomarker[a]	pg/mL	2.54	6	2.60	2.84	.02
IL-6 biomarker[a]	pg/mL	2.54	12	2.48	2.69	.02
SPPB[a]	Score	7.5	6	8.7	8.0	<.001
SPPB[a]	Score	7.5	12	8.5	7.9	<.001
400-m walk speed[a]	m/s	0.86	6	0.87	0.84	<.001
400-m walk speed[a]	m/s	0.86	12	0.85	0.82	<.001
Cognitive function	Mean global composite z score		24	−0.052	−0.081	.40
Hippocampal volume, left (n = 24)	Voxels	PA = 3.57HE = 3.46	24	3.83	3.60	.026

Abbreviations: HE, health education; IL, interleukin; PA, physical activity; SPPB, Short Physical Performance Battery.
[a]Lifestyle Interventions and Independence for Elders-Pilot.

interventions included a structured, moderate-intensity physical activity program (n = 818) involving aerobic, resistance, and flexibility training (twice per week center based and 3-4 times per week home based) and a health education program (n = 817) with workshops/lectures on topics relevant to older adults and upper extremity stretching.[13]

Here we summarize selected findings from the LIFE studies on a broad range of outcomes, including major health, frailty, cost-effectiveness, behavioral, biomarkers, and imaging. Finally, we outline the legacy of the LIFE studies.

MAJOR HEALTH OUTCOMES

The LIFE Study showed that, compared with the health education program, the physical activity program:

- Reduced the risk of the primary outcome of first occurrence of MMD (hazard ratio [HR] = 0.82; 95% confidence interval [CI] = 0.69-0.98; *P* = .03), of persistent MMD (HR = 0.72; 95% CI = 0.57-0.91; *P* = .006), and of the combined outcome of MMD or death (HR = 0.82; 95% CI = 0.70-0.97; *P* = .02; Figures 2 and 3)[14]; the benefit of physical activity on MMD was particularly evident among participants who were more physically impaired at baseline, with an SPPB score of less than 8 (HR = 0.75; 95% CI = 0.60-0.94; Figure 2)[14];
- Was associated with nonsignificantly higher serious adverse events (risk ratio [RR] = 1.08; 95% CI = 0.98-1.20;
- Reduced the MMD burden over an extended period of time, yielding an RR of 0.75 (95% CI = 0.64-0.89; Figure 3)[15];
- Did not produce significant effects on global or domain-specific cognitive function (Table 1),[16] the combined outcome of mild cognitive impairment or dementia (Figure 3),[16] cardiovascular events (Figure 3),[17] or serious fall injuries (Figure 3)[18]; power to detect only large effects may partially explain these results; and
- One year after cessation of the interventions, the two groups reported similar levels of physical activity, suggesting that a continued behavioral intervention is needed to sustain higher levels of physical activity.[19] National Institutes of Health (NIH) applications to further extend follow-up of the LIFE cohort did not achieve a fundable score.

FRAILTY

In the LIFE-Pilot, the physical activity intervention reduced the 12-month prevalence of frailty compared with health education (10.0% [95% CI = 6.5% to 15.1%] vs 19.1% [95% CI = 13.9%-15.6%]; *P* = .01),[20] when frailty was defined with the Fried criteria.[21] Among these frailty criteria, sedentary behavior was the one most affected by the intervention. Similar results were found in the larger LIFE Study (A. Trombetti, 2017, unpublished data). The Fried criteria may not be appropriate for the frailty outcome in LIFE because they include self-reported low physical activity. When frailty was defined according to the Study of Fractures criteria,[22] which do not include low physical activity, the effect of physical activity on frailty in the LIFE Study was not statistically significant (Table 1).[23]

COST-EFFECTIVENESS

Over 2.6 years of follow-up, the average LIFE intervention cost per participant was $3302 for the physical activity group and $1001 for the health education group.[24] Compared to health education, physical activity accrued incremental cost-effectiveness ratios of $42 376 per MMD prevented and $49 167 per quality-adjusted life year (QALY) gained. These costs per QALY gained are comparable to those found in other studies for many commonly recommended medical treatments, such as, for example, similar to the inflation-adjusted (35%) figure of $42 541/QALY found in the Diabetes Prevention Program study.[24]

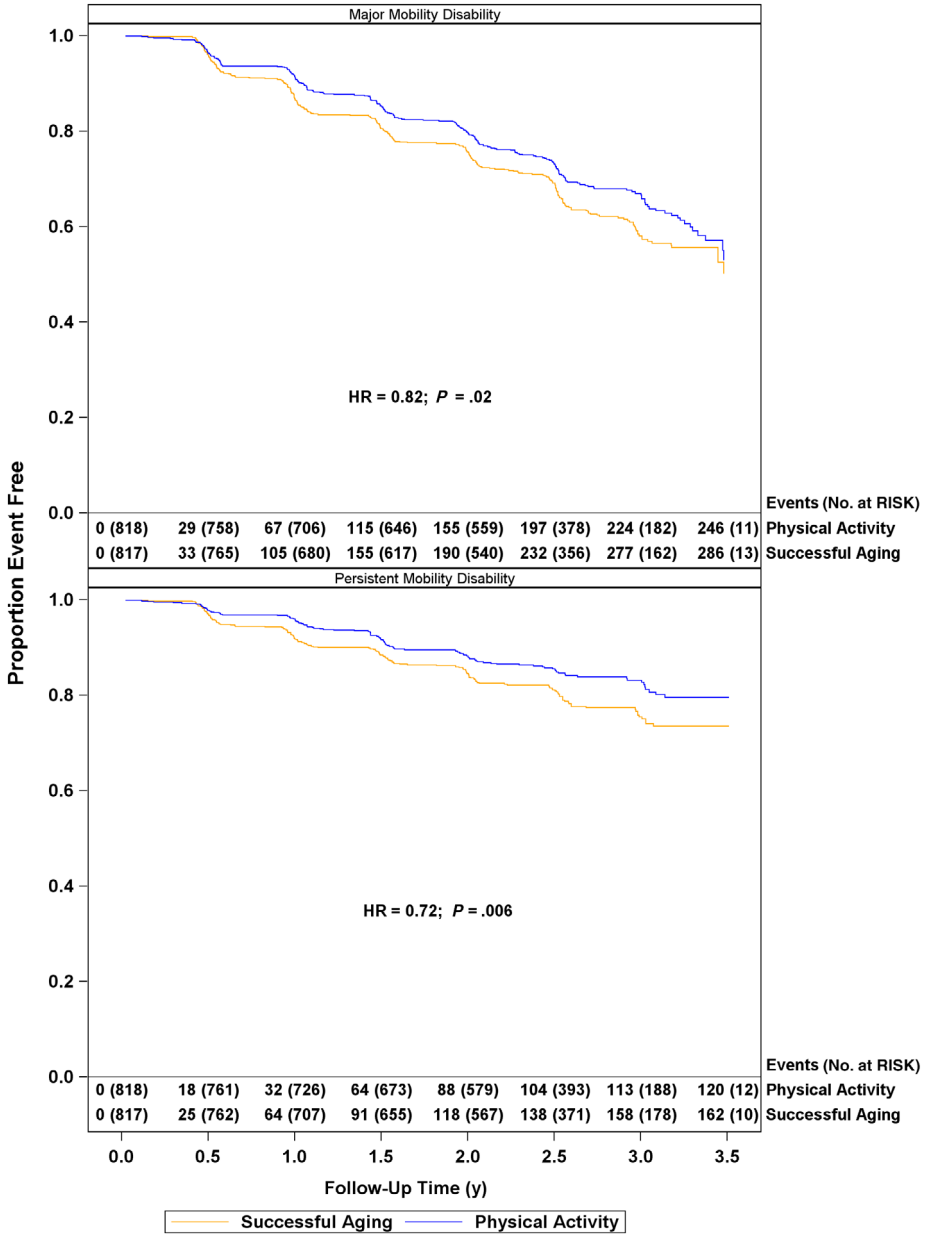

Figure 2. Reproduced with permission from *JAMA*.[15] The effect of a moderate physical activity intervention on the onset of major mobility disability and persistent mobility disability: the Lifestyle Interventions and Independence for Elders Study. Kaplan-Meier plots of major mobility disability occurrence and persistent mobility disability occurrence are presented in the top and bottom panels, respectively. The graph for major mobility disability was truncated at 3.5 years, and the health education group had four additional failures between 3.5 and 3.6 years of follow-up. Number of events represents cumulative events, and adjusted hazard ratios (HRs) and *P* values are from proportional hazards regression models. [Color figure can be viewed at wileyonlinelibrary.com]

BEHAVIORAL OUTCOMES

In the LIFE-Pilot, participants randomized to the physical activity intervention improved self-efficacy for a 400-m walk and satisfaction with physical functioning (Table 1).[25]

Disproportionate amounts of sedentary time, independent of the total amount of physical activity engaged in, are associated with a broad range of adverse health outcomes. In the LIFE Study, compared with health education, the physical activity intervention was associated with a small, but statistically significant, reduction in sedentary time measured by accelerometry.[26] However, at 6 months of follow-up, the group difference was only 9 min/d (630 vs 639 minutes; $P = .002$), suggesting that specific interventions are needed to achieve major reductions in sedentary behaviors (Table 1).

BIOMARKERS

In the LIFE-Pilot, compared with health education, physical activity resulted in lower plasma interleukin-6 (2.48 vs

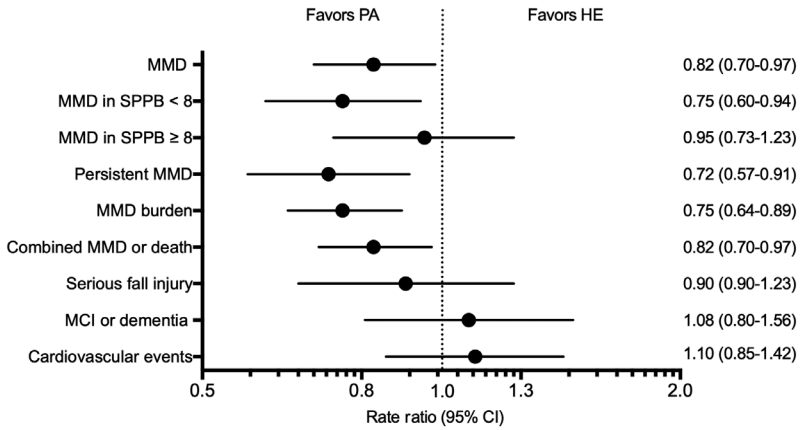

Figure 3. Forest plot, hazard ratio, and 95% confidence interval for the primary outcome of major mobility disability (MMD) and select dichotomous outcomes. HE indicates health education; MCI, mild cognitive impairment; PA, physical activity; SPPB, Short Physical Performance Battery.

2.69 pg/mL; $P = .02$; Table 1).[27] This effect was more evident in participants with an SPPB score of less than 8 (2.44 vs 3.06 pg/mL; $P = .005$).

In the LIFE-Pilot, the endogenous peptide apelin was positively correlated with SPPB score increases with physical activity ($r^2 = 0.34$; $P = .0001$).[28]

A replication and meta-analysis of the LIFE-Pilot, LIFE, and the Health, Aging, and Body Composition cohort identified several mitochondrial DNA (mtDNA) variants that are associated with variation in walking speed.[29] Another analysis of the LIFE-Pilot and LIFE studies identified mtDNA-encoded variants that are associated with variations in systolic and mean arterial pressure.[30]

IMAGING

In a subset of the LIFE-Pilot (n = 42), the physical activity intervention almost completely averted the midthigh skeletal muscle intermuscle fat infiltration that occurred in the health education group after 12 months (Table 1).[31] In another LIFE-Pilot subgroup (n = 27) who underwent functional magnetic resonance imaging 2 years after completion of the interventions, participants who were randomized to physical activity and who reported greater physical activity had higher brain activation within regions important for processing speed compared with those randomized to health education who remained sedentary.[32]

In a LIFE Study subset (n = 24), the physical activity group had a significantly larger left hippocampal volume compared with the health education group (3.83 vs 3.60 voxels; $P = .026$) after 2 years of intervention (Table 1).[33]

CHALLENGES

The implementation of the LIFE studies faced several challenges in developing a definitive study for the prevention of mobility disability. Below is an outline of the main factors that investigators had to resolve to successfully implement the LIFE Study.

Selection of Clinical Sites

The key criteria for selecting the study sites were (1) a track record of successfully recruiting from the community and retaining older persons who are at risk of disability; (2) a track record of delivering physical activity interventions; (3) expertise in randomized clinical trials, geriatric outcomes, exercise physiology, and behavioral interventions; (4) resources to conduct the physical activity walking interventions and the assessments; and (5) ability to work in a multidisciplinary team environment.

Primary Outcome

Early on, we faced the decision of whether to use a self-reported mobility disability outcome or an objective outcome. We decided that for a study this large and important we could make a much stronger case to the general medical community and the public if we had an objective, standardized outcome. The National Institute on Aging (NIA) also advocated for an objectively measured outcome for a multicenter study of that size.

The choice of the primary outcome to operationalize mobility disability represented a major challenge. MMD,[13,14] defined as inability to walk 0.25 miles or 400 m, was measured in the LIFE-Pilot and was our preferred primary outcome for the main trial. MMD is of major public health significance. Ability to walk 0.25 miles is measured in the US census[34] and in most epidemiologic surveys.[35] The MMD outcome, based on the 400-m walk test, is a feasible, objective, reliable,[5] well-validated, and important clinical and public health outcome in older people,[2,13,14] which we successfully implemented in the LIFE-Pilot and LIFE.[36,37] We have shown it to be a more efficient outcome for clinical trials than self-reported disability or the SPPB.[9] Public health agencies use ability to walk 0.25 miles or 400 m to define need and policy impact of interventions.[35] Finally, people reporting the inability to walk 400 m incur higher healthcare costs of $4000 per person per year, compared with those not reporting inability to walk 400 m.[2,35,38-40] MMD was operationalized as the inability to complete a 400-m walk test within 15 minutes without sitting or help of another person or walker.[13]

Completing the walk in greater than 15 minutes would be in an extremely slow pace (<0.45 m/s), which is of little utility in daily life.[41] A higher cut point (30 or 60 minutes) makes the assessment impractical and would not add to the clinical significance of the outcome. The time to walk 400 m and the ability to complete the test provided data to test effects of the interventions resulting from both attenuation of decline and increase in walking speed. We hypothesized that, compared with health education, the physical activity intervention will reduce the risk of reaching the MMD outcome.

When the 400-m walk test could not be administered, particularly when participants could only be evaluated in the clinic or in their homes, we took a conservative approach to adjudicating MMD based on objective inability to walk 4 m in 10 seconds or less, or self-, proxy-, or medical record–reported inability to walk across a room. We developed a detailed manual of procedures to define specific criteria for meeting this end point with high specificity. In LIFE, only 13.8% of MMD cases were determined by these alternative measures.

The 6-minute walk test (6MWT)[42-45] was considered as an alternative outcome.[45-48] The 6MWT asks participants to cover as much ground as possible in 6 minutes, and it estimates VO_2max, an important component of mobility. The 400-m walk and the 6MWT are highly inversely correlated. Those who complete a "fast pace" 6 minutes and "fast pace" 400-m test complete them in approximately the same amount of time/distance.[49] Both tests are related to VO_2max.[49] Both tests have well-defined metrics for meaningful change.[11,44] The 6MWT has several safety exclusions,[43] while there are no exclusions for attempting the 400-m walk at usual pace in people who are ambulatory. In both cases, noncompletion will occur. To address noncompletion (not attending visit, home bound), we included a 4-m walk test, which can be conducted during a home visit and used for MMD adjudication.[2,11] We favored the 400-m walk test for its established relationship to mobility disability as a dichotomous outcome, the public health relevance, and the well-developed protocols to adjudicate MMD by committee, which are not available for the 6MWT, and its established metrics for meaningful change.

We calculated the power for effect sizes ranging from 20% to 25% relative effects on MMD. Based on perceived clinical importance and public health relevance, it was important to have reasonable power to detect a relative effect size in this range. A sensitivity analysis was performed to adjust relative effect sizes for potential drop in/dropout and nonadherence. Ultimately, a total sample size of 1600 participants was planned, recruited, and followed for an average of 2.6 years.

Study Population

We targeted a population at high risk of disability who is often excluded from large multicenter trials. That raised important issues regarding retention and adherence, specifically because of frequent health problems and hospitalizations. A higher adherence would likely result in greater benefits of physical activity. We devised plans to perform follow-up visits at home or institution for participants who could not come to the clinic. A protocol was put in place to reengage the physical activity intervention in case of intercurrent illness that may have compromised adherence. In case of suspension of the intervention, the physical activity goals were reevaluated based on participant's illness and physical condition on reentry into the intervention.

Physical Activity Intervention

We wanted to maximize the public health impact of the LIFE Study. Thus, we chose a physical activity intervention that did not require any special equipment, such as treadmills or weight machines. The physical activity was a simple intervention involving walking, ankle weights, balance exercises, and stretching, which could be implemented virtually anywhere.

Funding

Obtaining funding for the main LIFE Study took 9 years (from 2000 to 2009) of negotiations with various funding agencies, primarily the NIH, production of preliminary data by means of secondary data analyses in existing databases, production of pilot data, multiple presentations at the NIA and the National Heart, Lung, and Blood Institute, and multiple formal grant submissions. Funding applications directed to industry and professional societies were unfruitful. Ultimately, high-quality preliminary data and persistence of the entire LIFE team were key factors that resulted in successful funding.

Lessons Learned

A highly cohesive, committed, and collaborative multidisciplinary team, along with the close guidance of the NIH project office, were key elements necessary for the development of this project over the long-term. The LIFE studies required the expertise of national leaders in a broad range of disciplines, including epidemiology, clinical trials, biostatistics, geriatrics, cardiology, neurology, behavioral sciences, biology, exercise physiology, and cost-effectiveness analyses. It was necessary for all to work in a coordinated team to achieve a common goal.

To ensure the coordinated functioning of the project, we organized several committees (Supplementary Material S1), which mainly met by conference call on a monthly basis.

The overall recruitment in the LIFE studies ahead of the planned time lines and benchmarks was the result of careful planning and preliminary modeling of inclusion/exclusion criteria from epidemiologic databases. The expected incidence rate of the MMD primary outcome was also the result of modeling the selection of the population at risk from epidemiologic studies, which resulted in the expected statistical power and significant results of the trial on the primary outcome.

LEGACY OF THE LIFE STUDIES

The LIFE studies have involved over 870 scientists, staff members, and trainees at 18 institutions throughout the United States (Supplementary Material S1). To date, these studies have generated a legacy of 109 peer-reviewed publications, including widely circulated general medicine and specialty journals, such as *JAMA*, *JAMA Cardiology*, *Annals of Internal Medicine*, *Archives of Internal Medicine*, *Nature Medicine*,

BMC Medicine, *Journals of Gerontology*, and the *Journal of the American Geriatrics Society* (Supplementary Table S1). A total of 19 ancillary studies took advantage of the data, biological samples, and resources of the LIFE studies (Table 2). At least 38 independently funded grants and clinical trials capitalized on the LIFE studies (Supplementary Table S2) by sharing preliminary data and study materials, including protocols, manuals of operations and procedures, recruitment materials,

Table 2. Ancillary Studies to LIFE and LIFE-P

Principal Investigator (Institution)	Title	Funding Source	Study
Thomas Buford, PhD (University of Florida)	Effects of a one-year physical activity program (LIFE-P) on serum C-terminal agrin fragment (CAF) concentrations[57]	NeurotuneAG (Switzerland)	LIFE-P
Christopher deFilippi, MD (University of Maryland)	Impact of moderate physical activity on cardiac specific biomarkers of stress and injury: support for modifying early heart failure phenotypes[58]	Roche Diagnostics Corporation	LIFE-P
Vonetta Dotson, PhD (University of Florida)	Physical activity and depressive symptoms in LIFE-P: effects of genetic polymorphisms[59]	NIA U01AG022376-07S1	LIFE-P
Cedric Dray, PhD (INSERM)	The effects of exercise on apelin[28]	INSERM (France)	LIFE-P
Tina J. Ellis Brinkley, PhD (Wake Forest University)	Genetic polymorphisms in the renin-angiotensin system and changes in physical function with exercise training[60]	Wake Forest OAIC and GCRC	LIFE-P
Bret Goodpaster, PhD (University of Pittsburgh)	Effects of exercise body composition in the elderly: the LIFE study (DXA body comp)[61]	NIA contract	LIFE-P
Bret Goodpaster, PhD (University of Pittsburgh)	Effects of exercise on muscle strength and quality in the elderly: the LIFE study[31]	University of Pittsburgh	LIFE-P
Denise Houston, PhD, RD (Wake Forest University)	Role of vitamin D status and VDR polymorphisms on physical function[62]	NIA K01AG030506	LIFE-P
Jeffrey Katula, PhD (Wake Forest University)	Complex mobility and executive function[63]	Wake Forest University	LIFE
Christine Liu, MD, MS (Tufts University)	The impact of chronic kidney disease on the effectiveness of physical activity in older adults[64]	Tufts University	LIFE and LIFE-P
Todd Manini, PhD (University of Florida)	mtDNA modifiers of the effect of exercise on cardiopulmonary and walking function in elders[29]	NIH/NHLBI R01HL121023	LIFE and LIFE-P
Barbara Nicklas, PhD (Wake Forest University)	Exercise and inflammatory risk factors for disability[27]	NIH R01AG027529	LIFE-P
Barbara Nicklas, PhD, and Xuewen Wang, PhD (Wake Forest University)	Effects of exercise training on prevalence of metabolic syndrome in the elderly[65]	American Heart Association	LIFE-P
Anne Newman, MD, MPH (University of Pittsburgh)	Napping and sleep practices of older adults: relationship to sleep duration and quality[66]	University of Pittsburgh	LIFE-P
Jack Rejeski, PhD (Wake Forest University)	Quantifying physical activity in the physical activity intervention using accelerometry[67]	Wake Forest University	LIFE
Caterina Rosano, MD, MPH (University of Pittsburgh)	Cerebral blood flow, structural brain characteristics, neuronal activation, and 2-year response to physical activity intervention in the LIFE participants[33]	NIA contract; Pittsburgh OAIC	LIFE
Caterina Rosano, MD, MPH (University of Pittsburgh)	A pilot study to measure the association between functional brain MRI activation and motor performance in the LIFE participants[32]	NIA contract	LIFE-P
Andrea Rosso, PhD, MPH (University of Pittsburgh)	Dopamine-related genes, physical activity adherence, and cognitive outcomes[68]	University of Pittsburgh	LIFE
Joshua Brown, PharmD, PhD (University of Florida)	LIFE's legacy: secondary data linkage to evaluate the long-term effects of the LIFE trial[69]	University of Florida OAIC	LIFE

Abbreviations: GCRC, General Clinical Research Center; LIFE, Lifestyle Interventions and Independence for Elders; LIFE-P, LIFE-Pilot; NHLBI, National Heart, Lung, and Blood Institute; NIA, National Institute on Aging; NIH, National Institutes of Health; OAIC, Older Americans Independence Center.

retention materials, biological samples, and other resources. These studies include, among others, the ENabling Reduction of Low-grade Inflammation in SEniors study to assess the effects on fish oil and losartan on mobility[50]; the SPRINT-T trial in Europe to assess the effects on the LIFE interventions and diet on MMD[51]; and the coordinating center for the MOTRPAC consortium to assess the molecular transducers of physical activity.[52] The LIFE studies facilitated the careers of 59 early career scientists (Supplementary Table S3) through publications, secondary analyses, ancillary studies, independent grants, and direct participation in the operations and experience at the LIFE Study sites. Today, many of these former early career scientists hold major leadership roles. The data and biological samples of the LIFE Study are now publicly available from a repository sponsored by the NIA (https://agingresearchbiobank.nia.nih.gov).

The results of the LIFE studies contributed to several public health recommendations for physical activity in older adults, including the US Department of Health and Human Services Physical Activity Guidelines for Americans,[53] the Asia-Pacific Clinical Practice Guidelines for the Management of Frailty,[54] and the Physical Activity Guidelines Advisory Committee guidelines.[55] The LIFE studies added to the scientific evidence, as indicated by high citation of the main articles[8,14] (625 and 738 citations, respectively, reported by Google Scholar on November 18, 2019), which likely have had an effect on the US population physical activity practices. The Centers for Disease Control and Prevention recently reported that the proportion of adults meeting minimum aerobic physical activity guideline (moderate intensity for ≥150 min/wk, vigorous intensity for ≥75 min/wk, or an equivalent combination) increased from 49.9% in 2013 (before the publication of the LIFE Study results) to 54.1% in 2017.[56]

Should we plan the LIFE Study today, we would likely focus on recruiting participants with an SPPB score of less than 8, as virtually all the physical activity benefit was accrued in this lower functioning group. We would also measure lower extremity strength and body composition.

CONCLUSION

The LIFE studies support the view that thorough planning, secondary analyses of data from existing studies, extensive pilot testing, and persistence are of pivotal importance to secure the success of a large multicenter phase 3 clinical trial. The LIFE studies have shown that older persons who are at high risk of disability and are traditionally excluded from large clinical trials can be successfully recruited, can be retained, and will adhere to behavioral interventions and physical and cognitive assessment protocols. The LIFE Study has demonstrated that a structured physical activity program is more effective than health education for preventing MMD. The LIFE studies and their related outcomes have generated a wealth of scientific findings and resources in geriatrics and gerontology to benefit the research community, trainees, clinicians, policy makers, and the general public. Large multicenter trials are needed to address important health questions in older adults. The LIFE Study provides an example of how not only the critical questions can be answered, but also of a major positive impact on early-stage scientists, on development of new innovative ideas, and on economy.

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Critical Revision of the Manuscript for Important Intellectual Content

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1: LIFE and LIFE-P Published Articles

Supplementary Table S2: Independently Funded Grants That Took Advantage of the LIFE Studies

Supplementary Table S3: LIFE and LIFE-P Early Career Scientists