



Research Article

Association of Intensive Lifestyle and Metformin Interventions With Frailty in the Diabetes Prevention Program Outcomes Study

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Abstract

Background: Frailty is a geriatric syndrome of decreased physiologic reserve and resistance to stressors that results in increased vulnerability to adverse health outcomes with aging. Diabetes and hyperglycemia are established risk factors for frailty. We sought to examine whether the odds of frailty among individuals at high risk of diabetes randomized to treatment with intensive lifestyle (ILS), metformin, or placebo differed after long-term follow-up.

Method: The sample comprised participants in the Diabetes Prevention Program (DPP) clinical trial, who continued follow-up in the DPP Outcomes Study (DPPOS) and completed frailty assessments in DPPOS Years 8 ($n = 2385$) and 10 ($n = 2289$), approximately 12 and 14 years after DPP randomization. Frailty was classified using Fried Frailty Phenotype criteria. GEE models adjusting for visit year with repeated measures pooled for Years 8 and 10 were used to estimate pairwise odds ratios (ORs) between ILS, metformin, and placebo for the outcomes of frail and prefrail versus nonfrail.

Results: Frailty prevalence by treatment group was ILS = 3.0%, metformin = 5.4%, placebo = 5.7% at Year 8, and ILS = 3.6%, metformin = 5.3%, placebo = 5.4% at Year 10. Odds ratios (95% CI) estimated with GEE models were ILS versus placebo, 0.62 (0.42–0.93), $p = .022$; metformin versus placebo, 0.99 (0.69–1.42), $p = .976$; and ILS versus metformin, 0.63 (0.42–0.94), $p = .022$. Odds of being frail versus nonfrail were 37% lower for ILS compared to metformin and placebo.

Conclusions: Early ILS intervention, at an average age of about 50 years, in persons at high risk of diabetes may reduce frailty prevalence in later life. Metformin may be ineffective in reducing frailty prevalence.

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Keywords: Behavioral modification, Geriatric syndromes, Pharmacotherapy, Prediabetes

Frailty is a geriatric syndrome characterized by decreased physiological reserve and resistance to stressors that result from progressive declines across multiple physiologic systems and increases vulnerability to adverse health outcomes (1). Frail older individuals are at

increased risk of death, disability, falls, hospitalization, and nursing home placement, accompanied by high health care costs. A systematic review of community-based studies in adults 65+ years old (1998–2010) found that the prevalence of physical frailty ranged

from 4% to 17%, with a weighted average prevalence of 9.9% (2). Diabetes, which affected 12 million, or 25.2%, of U.S. adults 65+ years old in 2015 (3), is a major risk factor for frailty (4,5). In a nationally representative sample of older adults, which characterized individuals as nonfrail, prefrail, and frail based on the Fried Frailty Phenotype (1), prevalence of diabetes was 2 times higher in those who were frail than in those who were nonfrail (35.5% vs 17.2%) and 1.5 times higher in those who were prefrail (25.5%) than in those who were not frail (6). Based on American Diabetes Association (ADA) criteria—fasting plasma glucose, 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) or HbA1c, 5.7%–6.4% (39–47 mmol/mol) (7)—prediabetes affected 48.3% of U.S. adults 65+ years old in 2015 (3). This high prevalence of prediabetes in U.S. older adults is of concern because hyperglycemia, even in the prediabetes range, has been associated with increased risk of incident frailty (8).

Screening for early frailty detection has been recommended for individuals with diabetes beginning at age 55 and continuing thereafter (4), but the majority of frailty interventions have been directed toward improving physical performance and outcomes in frail older adults rather than preventing frailty onset or reducing frailty severity. Various exercise interventions have demonstrated beneficial effects on gait speed, balance, muscle strength, and incidence of falls among physically frail older adults, although the optimal type, frequency, and duration of exercise are still unclear (9,10). Pharmacologic interventions are in the early stages of development (11), but a randomized controlled trial is currently being conducted to examine whether metformin can prevent frailty in 65+-year-old individuals with prediabetes (clinicaltrials.gov identifier, NCT02570672) (12). The Diabetes Prevention Program (DPP) demonstrated that both an intensive lifestyle (ILS) intervention (comprised of both a weight loss and physical activity goal) and metformin relative to placebo were effective in reducing the incidence of diabetes in persons at high risk of this disease (13). Long-term follow-up of DPP participants has continued in the Diabetes Prevention Program Outcomes Study (DPPOS) and has shown a sustained impact of these interventions on prevention or delay of diabetes onset (14). The present study aims to examine whether the odds of frailty measured after long-term follow-up in Years 8 and 10 of the DPPOS (approximately 12 and 14 years following DPP randomization) differed between the DPP intervention arms.

Method

Design

This study was a long-term follow-up of a clinical trial that examined the association of DPP intervention arms with frailty in the DPPOS. Details of the eligibility criteria, study design, and methods of the DPP (13) and DPPOS (14) have been reported previously. Briefly, the DPP randomized 3234 participants at high risk of diabetes and enrolled between 1996 and 1999 to 3 interventions: ILS ($n = 1079$), metformin ($n = 1073$), or placebo ($n = 1082$). The blinded treatment phase lasted an average of 2.8 years and was stopped by the NIDDK on the recommendation of the Data Safety and Monitoring Board in July 2001, 1 year early, because of proven efficacy. ILS reduced the incidence of diabetes by 58% and metformin by 31% compared with placebo. A 13-month bridge period took place between August 2001 and August 2002. DPPOS began in Fall 2002. Frailty was assessed from July 2009 to October 2010 (DPPOS Year 8) and from

July 2011 to October 2012 (DPPOS Year 10), approximately 12 and 14 years after DPP randomization.

Participants

At study entry, participants were required to be ≥ 25 years old, have fasting plasma glucose 95–125 mg/dL (5.3 to <7.0 mmol/L) and 2-hour post-load glucose of 140–199 mg/dL (7.8 to <11.1 mmol/L), and body mass index (BMI) of ≥ 24 kg/m² (≥ 22 kg/m² in Asian Americans). All ethnic groups were included with a goal of enrolling up to 50% of participants from high risk populations. Persons taking medications known to alter glucose tolerance or who had illnesses that could reduce their life expectancy or their ability to participate in the trial were excluded. All participants gave written informed consent prior to screening in accord with the Declaration of Helsinki and the guidelines of each center's institutional review board.

Study Interventions

The ILS group underwent an intensive behavioral modification program with the specific goals of (i) $\geq 7\%$ loss of body weight from baseline and maintaining that weight loss, with a dietary fat goal of $<25\%$ of calories from fat and a calorie intake goal of 1200–1800 kcal/d; and (ii) achievement and maintenance of ≥ 150 min/wk of moderate-intensity physical activity similar to a brisk walk (minimum goal). The ILS structure included a 16-session core curriculum (over 24 weeks), a long-term maintenance program, supervision by a case manager, and access to lifestyle support staff, that is, dietitian, behavior counselor, and exercise specialist. The average duration of the intensive phase treatment was 3.2 years. The Core Curriculum provided education and training in diet and exercise and behavior modification skills, with emphasis on self-monitoring techniques; goal-setting; problem-solving; individualizing programs; self-regulation, and social support; and frequent contact with a case manager and DPP support staff. Sites were instructed to offer supervised physical activity sessions twice weekly, but attendance was optional. A detailed description of the ILS protocol has been reported (15). The Post Core Program included self-monitoring and other behavioral strategies, monthly visits with a requirement to be seen in person at least every 2 months, periodic group classes and motivational campaigns, and toolbox strategies that included providing exercise videotapes and pedometers as well as enrollment in a health club or cooking class. The metformin group received 850 mg of twice per day, and the placebo group received a matching placebo tablet metformin twice per day. Both the metformin and placebo groups also received standard lifestyle recommendations in the form of written information and an annual 20–30-minute individual session.

Continued follow-up in DPPOS was open to all active DPP participants and 88% enrolled. Follow-up included 910 participants from the ILS arm, 924 from the metformin arm, and 932 from the placebo arm. Because of the substantial reduction in diabetes incidence from ILS in the DPP, all 3 groups were offered a Healthy Lifestyle Program (HELP) comprised of 16 group sessions during the 13-month bridge period between DPP and DPPOS (16). Higher levels of session participation among the placebo and metformin groups were paralleled by significant weight loss, but overall weight loss remained higher in the ILS group (see [Supplementary Table 1](#)). Further, during the DPPOS continuation, quarterly group lifestyle sessions continued to be offered to all 3 groups, with ILS receiving 2 additional lifestyle booster sessions per year that emphasized multicomponent lifestyle self-management. The original metformin group continued to receive metformin treatment, with participants unmasked to the assignment.

Measurements

Frailty assessment

Frailty was classified using the 5 standardized Fried Frailty Phenotype criteria (1). Slow walking speed was measured as the slowest 20% of participants on a 15-foot walk test standardized by sex and height. Weak grip strength was measured as the weakest 20% of participants using a hand-held dynamometer standardized by sex and BMI. Low physical activity was measured as the lowest 20% of participants on physical activity levels as determined by the Modifiable Activity Questionnaire (MAQ; in MET-h/wk) (17) standardized by sex. Exhaustion was assessed by self-report on questions from either the Beck Depression Inventory (BDI) (18) or the Center for Epidemiologic Studies Depression (CES-D) scale (19). Unintentional weight loss was assessed by self-report of unexplained weight loss in the past 12 months and measured weight loss ≥ 10 pounds at the annual visit. These criteria are used to classify 3 frailty stages based on the number of criteria present: 0 = nonfrail, 1 or 2 = prefrail, and 3+ = frail. DPPOS 20%ile frailty cut points and detailed information about assessment of individual frailty characteristics is provided in the [Supplementary Appendix 1](#).

Other measures

Baseline characteristics were compared by DPP treatment arms among participants who completed frailty assessments in DPPOS Year 8 to establish that balance was maintained among those who underwent frailty testing. Demographic variables included age, sex, race/ethnic group (white, African American, Hispanic American, Asian American, and American Indian), and years of education. Other measures assessed included BMI, metabolic variables (fasting glucose, glycosylated hemoglobin [HbA_{1c}]), cardiovascular risk factors (systolic and diastolic blood pressure), leisure-time physical activity, SF-36 physical and mental components, and the BDI. At DPPOS Year 8, HbA_{1c} area under the curve (AUC) was calculated as the average of all available HbA_{1c} measures beginning with DPP randomization; metformin exposure in years was also calculated.

Statistical Methods

Descriptive statistics of participant characteristics by DPP intervention arm at DPPOS Year 8 were performed using analysis of variance (ANOVA) for continuous variables and chi-squared tests for categorical variables. Generalized estimating equation (GEE) models adjusting for visit year with pooled data from DPPOS Years 8 and 10 treated as repeated measures were used to estimate pairwise odds ratios between ILS, metformin, and placebo for the outcomes of frail and prefrail versus nonfrail. Pairwise odds ratios were calculated for ILS and metformin versus placebo as the referent, and for ILS versus metformin as the referent. Similar GEE models were also used to estimate the odds ratios between age groups, sex groups, race/ethnic groups, and incident diabetes versus none for the outcome of frail versus nonfrail. The covariance structure used for the GEE models was autoregressive with order 1, that is, AR(1).

A flowchart was constructed to show timelines and subject participation in the various study phases from DPP randomization to DPPOS Year 8 and 10 frailty assessments ([Supplementary Table 1](#)). Attrition analyses were performed separately for the period from DPP randomization to DPPOS Year 8 and from DPPOS Year 8 to 10. Completers and dropouts at DPPOS Year 8 were compared on DPP baseline characteristics; completers and dropouts at DPPOS Year 10 were compared on Year 8 characteristics. Analyses were performed separately by treatment arms using ANOVA for continuous

variables, or Wilcoxon/Kruskal–Wallis tests when distributions were not normal, and Pearson's chi-squared, or Fisher's exact test when numbers were small, for categorical variables. The GEE models described above to estimate pairwise treatment odds ratios using pooled data from Years 8 and 10 were also repeated using the Last Observation Carried Forward (LOCF) to replace frailty status (nonfrail, prefrail, frail) of Year 10 dropouts. All analyses were performed using SAS version 9.4 (SAS Institute, Inc.). Bonferroni adjustment of p -values for multiple comparisons was used as appropriate.

Results

A total of 2385 participants completed frailty assessments at DPPOS Year 8; of these, 2285 also completed frailty assessments at Year 10. Average age at randomization of participants who completed frailty assessments at DPPOS Year 8 was 51.1 ± 10.0 years, and there were no significant differences in DPP baseline characteristics among the DPP treatment arms ([Table 1](#)). At the time of the initial frailty assessment (DPPOS Year 8) participants' average age was 63.2 ± 9.93 , and time from randomization was 12.0 ± 0.77 years ([Table 2](#)). Fasting glucose levels, HbA_{1c} AUC, BMI, diabetes prevalence, and diabetes duration were lower in both the ILS and metformin arms compared with the placebo arm ([Table 2](#)). Mean HbA_{1c} during follow-up was virtually identical in the ILS and metformin arms, while diabetes prevalence was 3.4% higher and mean duration of diabetes was 0.69 years longer in the metformin arm compared to the ILS arm. Years of metformin exposure was 6 times greater in the metformin group than in the placebo group and 9 times greater than in the ILS group. There were no differences among DPP treatment arms at DPPOS Year 8 in cholesterol levels, leisure-time physical activity, SF-36 physical or mental component scores, or the BDI.

Overall, the proportion of participants classified as nonfrail, prefrail, and frail was 50.2%, 45.1%, and 4.7%, respectively, in DPPOS Year 8 and 51.1%, 44.1%, and 4.8%, respectively, in DPPOS Year 10, ([Table 3](#)). The proportion of individuals classified as frail in Year 8 was 1.8 and 1.9 times higher, respectively, in the metformin (5.4%) and placebo (5.7%) arms, than in the ILS arm (3.0%) and in Year 10 was 1.5 times higher in both the metformin (5.3%) and placebo (5.4%) arms than in the ILS arm (3.6%). These treatment arm differences examined separately at Years 8 and 10, however, did not reach statistical significance.

When pairwise treatment odds ratios for the outcome of frail/prefrail versus nonfrail were estimated using GEE models adjusted for visit year with pooled repeated measures from Years 8 and 10, however, pairwise odds ratios between ILS, metformin, and placebo for the outcomes of frail/prefrail versus nonfrail ([Table 4](#)) were 0.62 (0.42–0.93), $p = .022$ for ILS versus placebo and 0.99 (0.69–1.42), $p = .976$ for metformin versus Placebo. The odds ratio for ILS versus metformin was 0.63 (0.42–0.94), $p = .024$. Pairwise treatment odds ratios for the outcome of prefrail versus nonfrail were not statistically significant. No single frailty characteristic drove the overall findings. Treatment effects on individual frailty characteristics are provided in [Supplementary Tables 2–4](#).

A multivariable GEE model adjusting for visit year and treatment arm with pooled data from DPPOS Years 8 and 10 treated as repeated measures was used to estimate odds ratios for the association between frailty/nonfrailty and age, sex, race/ethnic groups, as well as incident diabetes versus none ([Table 5](#)). Younger age groups relative to the oldest and men relative to women had significantly lower odds of being frail. Relative to the White reference group, all

Table 1. Characteristics at the Time of Randomization, by Treatment Arm, for Participants in the Diabetes Prevention Program Outcomes Study (DPPOS) Who Underwent Frailty Assessments at Year 8

Characteristic	Lifestyle (<i>n</i> = 787)	Metformin (<i>n</i> = 803)	Placebo (<i>n</i> = 795)	Overall (<i>n</i> = 2385)
Age at randomization (years)	51.3 (10.6)	51.5 (9.67)	50.5 (9.70)	51.1 (10.0)
Women (%)	67.9	66.1	68.9	67.6
Race/ethnicity (%)				
White	53.5	55.5	53.8	54.3
African American	19.7	21.3	20.6	20.5
Hispanic	14.5	14.6	14.7	14.6
American Indian	6.2	5.1	6.0	5.8
Asian	6.1	3.5	4.8	4.8
Education (%)				
≤12 years	74.1	71.5	75.0	73.5
13–16 years	25.9	28.5	25.0	26.5
Fasting glucose (mg/dL)	106 (8.08)	107 (8.61)	107 (8.62)	107 (8.44)
HbA1c %	5.91 (0.49)	5.92 (0.50)	5.93 (0.50)	5.92 (0.50)
BMI (kg/m ²)	33.5 (6.40)	33.7 (6.45)	34.0 (6.59)	33.7 (6.48)
Systolic blood pressure (mm Hg)	123 (14.7)	124 (15.0)	123 (14.4)	123 (14.7)
Diastolic blood pressure (mm Hg)	78.2 (9.27)	78.1 (9.49)	78.0 (9.26)	78.1 (9.34)
Leisure physical activity (MET-h/wk)	15.6 (21.6)	17.0 (22.5)	17.5 (32.3)	16.7 (25.9)
MOS SF-36 physical component	50.7 (6.79)	50.1 (7.17)	50.4 (7.22)	50.4 (7.07)
MOS SF-36 mental component	53.9 (7.12)	54.1 (7.62)	54.2 (6.77)	54.1 (7.18)
Beck Depression Inventory (BDI)	4.42 (4.37)	4.35 (4.26)	4.42 (4.45)	4.39 (4.36)

Note. BMI = body mass index; HbA1c = glycosylated hemoglobin; MET = rate of energy expenditure while at rest; MOS SF = Medical Outcomes Study Short Form. Data for continuous variables are presented as mean (*SD*). Data for categorical variables are presented as percentage. There were no significant treatment arm differences.

the minority race/ethnic groups except the Asian group had higher odds of being frail. Individuals with incident diabetes during DPP/DPPOS compared with those who remained nondiabetic were 1.46 times more likely to be frail at long-term DPPOS follow-up.

Analyses examining differential attrition across treatment groups are provided in [Supplementary Tables 5–11](#). There were no significant differences in DPP baseline characteristics in the placebo group between Year 8 dropouts and completers. In both the ILS and metformin groups, the only significant difference in baseline characteristics between Year 8 dropouts and completers was mean age at randomization; mean age (*SD*) of dropouts versus completers was 49.2 (11.9) versus 51.5 (10.3) in the ILS group and 48.8 (12.8) versus 51.3 (10.6) in the metformin group.

Year 10 dropouts included 42 participants in the ILS group, 33 in the metformin group, and 21 in the placebo group. There were no significant differences between Year 10 dropouts and completers on any Year 8 characteristics, including frailty status, in either the metformin or placebo group. In the ILS group, however, Year 10 dropouts had a significantly lower mean (*SD*) physical component summary score (39.9 [10.6] vs 47.2 [9.24]) and significantly higher mean (*SD*) BDI score (7.47 [6.22] vs 4.42 [5.20]). Pairwise odds ratios for the outcome of frail/prefrail versus nonfrail estimated using the GEE models previously described but with LOCF replacement of frailty status for Year 10 dropouts were very similar to those obtained using observed data.

Discussion

Among DPPOS participants who completed frailty assessments in Years 8 and 10, approximately 12–14 years after DPP randomization, there was no difference in the odds of frailty between the metformin and placebo arms. In contrast, those in the ILS arm

compared with those in both the metformin and placebo arms had 37% lower odds of frailty. Frailty odds varied across demographic groups: younger ages at DPP baseline (vs older ages) and male sex (vs female) were associated with lower odds of being frail; and African American, Hispanic, and American Indian race/ethnicity (vs White) were associated with higher odds of being frail. In addition, participants who developed diabetes during the DPP/DPPOS compared with those who remained free of diabetes had about 1.5 times higher odds of being frail after long-term follow-up in the DPPOS.

Interestingly, there were no significant treatment group differences in prevalence of individual frailty characteristics in DPPOS Year 8 or 10 or any significant pairwise treatment odds ratios for individual frailty characteristics when GEE analyses were performed with adjustment for visit year and using pooled data from DPPOS Years 8 and 10 treated as repeated measures. This suggests that rather than preventing the development of any individual frailty characteristic, ILS prevented the accumulation of 3 or more frailty characteristics considered to constitute the stage of frank frailty.

While most studies of exercise interventions for frailty have focused on improving physical function in already frail older adults (9,10), 2 randomized controlled trials examined the effects of exercise interventions on frailty status over 1 year. One measured frailty status using the Fried Phenotype (20), the other using the modified Physical Performance Test (21). The first study conducted in sedentary community-dwelling adults, 70–89 years old, at increased risk of mobility disability. It found that a physical activity intervention focused on achieving a goal of walking at least 150 min/wk resulted in significantly lower frailty prevalence (10% vs 19%, $p = .01$) compared to a successful aging health education group and that there was a significant difference in mean number of frailty criteria ($\Delta = -0.27$, $p = .01$). The second study conducted in obese adults 65+ years old found that an intervention combining weight loss and

Table 2. Characteristics of Participants, by Treatment Arm, When They Underwent Frailty Assessments at Year 8 of the Diabetes Prevention Program Outcomes Study (DPPOS)

Characteristic	Lifestyle	Metformin	Placebo	Overall
	(n = 750)	(n = 779)	(n = 756)	(n = 2285)
Age at DPPOS Year 8 (years)	63.3 (10.6)	63.6 (9.63)	62.6 (9.49)	63.2 (9.93)
Time from randomization (years)	12.0 (0.78)	12.0 (0.78)	12.0 (0.76)	12.0 (0.77)
Fasting glucose (mg/dL)****	121 (30.4)	116 (27.2)	124 (33.9)	120 (30.7)
HbA1c %	6.58 (1.28)	6.38 (1.11)	6.49 (1.25)	6.48 (1.22)
HbA1c % mean during follow-up****	5.93 (0.58)	5.93 (0.57)	6.05 (0.65)	5.97 (0.60)
BMI (kg/m ²)*	32.5 (6.86)	32.8 (6.86)	33.5 (6.97)	33.0 (6.91)
Systolic blood pressure (mm Hg)	120 (13.9)	121 (13.6)	121 (14.2)	121 (13.9)
Diastolic blood pressure (mm Hg)	71.4 (9.43)	71.7 (9.64)	72.1 (9.39)	71.7 (9.49)
Diabetes prevalence (%)****	46.9	50.3	57.8	51.7%
Duration of diabetes (years)****	2.97 (3.90)	3.66 (4.35)	4.46 (4.59)	3.70 (4.33)
Time of metformin exposure (years)****	0.96 (2.03)	8.73 (4.16)	1.43 (2.51)	3.76 (4.70)
Leisure physical activity (MET-h/wk)	16.9 (19.6)	15.6 (20.5)	16.1 (19.5)	16.2 (19.9)
MOS SF-36 Physical subscale	46.9 (9.43)	46.8 (9.63)	46.6 (9.51)	46.8 (9.52)
MOS SF-36 Mental subscale	53.5 (8.94)	53.7 (8.57)	53.7(9.10)	53.6 (8.86)
Beck Depression Inventory	4.55 (5.28)	4.51 (4.88)	4.48 (4.97)	4.52 (5.04)

Notes: BMI = body mass index; HbA1c = glycosylated hemoglobin; MET = rate of energy expenditure while at rest; MOS SF = Medical Outcomes Study Short Form. Data for continuous variables are presented as Mean (SD). Data for categorical variables are presented as percentage.

p < .01. **p < .0001.

Table 3. Frailty Status in Years 8 and 10 of the Diabetes Prevention Program Outcomes Study (DPPOS) by Treatment Group

Characteristics	Lifestyle	Metformin	Placebo	Overall
Year 8	(n = 787)	(n = 803)	(n = 795)	(n = 2385)
Year 10	(n = 745)	(n = 770)	(n = 774)	(n = 2289)
Nonfrail (%)				
Year 8	50.2	48.8	51.6	50.2
Year 10	50.1	52.2	50.9	51.1
Prefrail (%)				
Year 8	46.8	45.8	42.8	45.1
Year 10	46.3	42.5	43.7	44.1
Frail (%)				
Year 8	3.0	5.4	5.7	4.7
Year 10	3.6	5.3	5.4	4.8

Note: There were no statistically significant treatment group differences in frailty status in either Year 8 or 10.

exercise (diet-exercise group) compared with interventions that included either weight loss (diet) or exercise alone had significantly greater improvements in the Physical Performance Test as well as VO_{2peak}, and showed consistent improvement in balance, gait, and strength relative to the diet and exercise groups. Further, the diet-exercise group compared with the diet group lost a similar amount of weight but had less reduction in lean mass and bone mineral density at the total hip.

In addition, a recent post hoc analysis of the Look AHEAD (Action for Health in Diabetes) randomized clinical trial of individuals aged 45–76 years with diabetes and overweight/obesity examined whether an intensive lifestyle intervention (ILI) designed to achieve weight loss and increased physical activity compared with a diabetes support and education (DSE) control group slowed the development of frailty as assessed by the deficit accumulation model, or Frailty Index (FI), over an 8-year period (22). A 38-item FI enriched

with deficits related to diabetes and obesity was measured at baseline and annually. Over the 8-year follow-up, mean (SE) differences between intervention groups averaged 5.4% (0.9%), and at year 8, significantly fewer ILI participants (54.5%) compared with DSE participants (60.9%) were classified as frail (FI > 0.21), p < .001.

The significant association of ILS with lower frailty prevalence after long-term follow-up in the DPPOS compared to placebo is consistent with results of the above studies. More extensive examination is warranted, however, to better understand why ILS was associated with lower frailty prevalence compared to metformin and why there was no significant difference in frailty prevalence between the metformin and placebo groups, especially given the pathophysiologic mechanisms common to diabetes and frailty (5,23–29) and metformin’s effectiveness in reducing incident diabetes in the DPP cohort.

Several studies suggest that metformin may have beneficial effects in preventing frailty. Metformin is an insulin sensitizer and has also been shown to reduce C-reactive protein (30). The longitudinal study of Osteoporotic Fractures in Men (MrOS) found that in those with impaired fasting glucose and type 2 diabetes, skeletal muscle loss was accelerated except among those taking insulin sensitizers (31). Further, the prospective Study of Osteoporotic Fractures found that women taking insulin sensitizers compared with those who were not had less decline in walk speed (32). A study of older Veterans with type 2 diabetes found that those treated with metformin versus sulfonylureas had 34% lower odds of frailty (OR: 0.66, CI: 0.61–0.71; p-value < .0001) (33). A systematic review of studies examining the potential geroprotective effect of metformin in humans concluded that the apparent reduction in diseases of aging (ie, cancer and cardiovascular disease) and all-cause mortality associated with metformin use suggest that metformin may be extending both life and health spans by serving as a geroprotective agent (34), and a recent review provides evidence that metformin may be an appropriate pharmaceutical intervention for targeting aging (35). The potential beneficial effects of metformin on frailty, however, were

Table 4. Odds Ratios for Pairwise Treatment Comparisons of Frail or Prefrail vs Nonfrail, Adjusted for Study Visit, in the Diabetes Prevention Outcomes Study (DPPOS)

Outcome	Treatment	Reference	Odds Ratio	95% Confidence Interval
Frail vs nonfrail	Lifestyle	Metformin*	0.629	0.420–0.942
	Lifestyle	Placebo*	0.625	0.419–0.934
	Metformin	Placebo	0.994	0.694–1.424
Prefrail vs nonfrail	Lifestyle	Metformin	1.058	0.893–1.254
	Lifestyle	Placebo	1.093	0.924–1.292
	Metformin	Placebo	1.033	0.873–1.221

Notes: Odds ratios are calculated using generalized estimating equations (GEE) with data from Years 8 and 10 pooled and treated as repeated measures. * $p < .05$.

Table 5. Odds Ratios for Demographic Characteristics and Incident Diabetes Comparing the Outcome of Frail vs Nonfrail in the Diabetes Prevention Program Outcomes Study (DPPOS)

Characteristic	Odds Ratio	95% Confidence Interval
Age (years)		
<45***	0.09	0.05–0.14
45–59***	0.16	0.11–0.23
60+	Reference	–
Sex		
Men**	0.61	0.42–0.88
Women	Reference	–
Race/ethnicity		
White	Reference	–
African American	2.11	1.37–3.25
Hispanic	3.07	1.99–4.74
American Indian	3.14	1.64–6.04
Asian	1.06	0.40–2.81
Incident diabetes		
Present*	1.458	1.03–2.07

Notes: Odds ratios are calculated using generalized estimating equations (GEE) with data from Years 8 and 10 pooled and treated as repeated measures. * $p < .05$. ** $p < .01$. *** $p < .0001$.

not observed in the DPPOS. Results of the ongoing randomized controlled trial of metformin to prevent frailty onset in 65+-year-old individuals with prediabetes (NCT02570672) will provide important evidence concerning the effectiveness of metformin in preventing frailty and the biological mechanisms involved (12).

This study has several limitations. Frailty data were not collected at DPP baseline; however, baseline frailty differences seem unlikely because demographic, biologic, and behavioral characteristics across groups were similar among those assessed for frailty at DPPOS Year 8. Because of the differences between the DPPOS cohort and the original cohort in which the frailty phenotype was operationalized, the frailty assessment used 20th percentile cutpoints from the DPPOS rather than the original study cohort (Supplementary Appendix 2 provides a comparison of the DPPOS and Cardiovascular Health Study [CHS] 20th percentile cutoffs). The questionnaires used to assess physical activity and exhaustion also differed from those in the original methods to define the frailty phenotype; this is a frequent limitation of secondary data analysis in studies using the frailty phenotype. The

DPP/DPPOS had weight loss as a goal; therefore, very few people reported unintentional weight loss at the time of frailty assessment. In addition, there is a possibility that some differences in attrition between the ILS and metformin and placebo treatment arms, Year 8 to Year 10, may have influenced study results, at least partially. Finally, treatment differences in physical activity and weight loss (BMI) were evaluated at DPPOS Year 8 only. Future research should include evaluation of weight loss and physical activity over the entire DPP/DPPOS intervention period.

The study also had several strengths. The study sample was diverse, including 45% racial/ethnic minorities and middle-aged participants (45–59 years old) as well as those 60 years and older. Potential effects of both a behavioral (ILS) and pharmaceutical intervention (metformin) on frailty prevalence were compared to those of a placebo; and these effects were examined after long-term follow-up, 12–14 years following randomization. The ILS intervention had the combined goal of weight loss and increased physical activity, which has been shown to be more effective in reducing frailty than weight loss or exercise alone (36).

Findings from the present study suggest that lifestyle intervention combining achievement and maintenance of weight loss and increased moderate-intensity physical activity when delivered early (average age of about 50 years) to persons at high risk of diabetes may reduce frailty 12–14 years later. Further research is needed to determine why metformin was not effective in reducing frailty prevalence in the DPP/DPPOS and whether it may prove effective in preventing frailty in the setting of a clinical trial specifically designed to address this question.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

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Author Contributions

H.P.H. contributed to the design of the study, interpreted the data, and drafted/revised the manuscript. Q.P. contributed to the design of the study, performed the statistical analyses, interpreted the data, and reviewed/edited the manuscript. H.F. J.A.L., J.P.C., E.M.V., S.H.G., A.M.K., and G.A.B. contributed to the design of the study, interpreted the data, and reviewed/edited the manuscript.

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