Effects of Body Composition and Leisure-time Physical Activity on Transitions in Physical Functioning in the Elderly

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Physical activity and body composition were examined with respect to variation in functional limitation over a 6-year period (four surveys conducted between 1994 and 2000) based on a cohort of 1,655 community-dwelling older women and men living in Sonoma, California. Measures of functional limitation and physical activity were based on standard self-report questions. Measures of body composition (lean mass, fat mass) were estimated from bioelectric impedance by using population-specific prediction equations derived from dual-energy x-ray absorptiometry. For women, a one-unit gain in lean mass:fat mass ratio reduced the report of limitation at all surveys 65.5% (95% confidence interval: 21.8, 87.4). A similar reduction was not observed for men; however, there was a 3% increase in the report of no limitation at any survey. The effect of high levels of physical activity reduced new functional limitation that occurred at the last survey by 36.8% (95% confidence interval: 0.0, 92.2) for men and 52.7% (95% confidence interval: 13.5, 91.9) for women. In summary, higher levels of physical activity appeared to reduce the risk of future functional limitation conditional on the level of functioning established early in the disablement process by lean mass:fat mass ratio.

aging; body composition; causality; exercise; stochastic processes

Abbreviations: L/F, ratio of lean body mass to fat mass; LTPA, leisure-time physical activity; MET, metabolic equivalent; MSM, marginal structural model.

Editor’s note: An invited commentary on this article appears on page 618, and the authors’ response is on page 621.

Body composition and physical activity have been observed to play an important role in the disablement process in the elderly (1–5). The disablement process is a model that depicts a pathway of events in aging adults that marks the gradual decline in bodily systems and links healthy functioning with functional limitation, disability, and mortality. As formulated, the process begins with underlying pathophysiologic abnormalities that develop into structural

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abnormalities in specific bodily systems (impairments). These impairments can impact the ability to function normally, with the potential consequence of a person’s inability to interact with and meet the demands of his or her social/physical environment (disability) (1). Recently, Stewart (6) suggested the refinement of the disablement model to include physiologic changes that accompany normal aging that contribute, independently of pathologic pathways, to the decline in bodily systems and physical fitness levels that leads to functional limitation and disability.

Previous studies have elaborated on the underlying risk factors (biologic, demographic, social, environmental attributes) that influence the underlying physiology and subsequent events along the pathway to disablement (1, 6, 7) and the complex network of intermediary factors that contribute to the disablement process (2). Of particular interest is the role of physical activity in the prevention of diseases that could lead to limitation or to reduction in the occurrence of functional limitation in healthy elders (8–12). Additionally, studies based on surrogates of underlying physiologic processes in the disablement process (measures of obesity in relation to impaired insulin metabolism) attempt to shed light on the roles and the potential mitigating effects of physical activity on the progress of disablement (4, 13).

Recently, leisure-time physical activity (LTPA) and ratio of lean body mass to fat mass (L/F) were examined for their associated and causal effects on self-reported functioning. In a cross-sectional analysis (3), L/F was associated with faster walking speed and improved functioning. Moreover, a relative measure of lean to fat mass, rather than lean body mass alone, was the more important factor related to physical performance and physical functioning. A subsequent longitudinal analysis evaluated the combined causal effects of L/F and LTPA on physical functioning (4); L/F had a greater effect than LTPA on the reduction of the log-odds of functional limitation, except in the presence of obesity. Those studies suggested that the beneficial effects of physical activity were most likely mediated through reduction of fat mass relative to lean mass. In addition, in the presence of obesity, it was found that improvement in muscle mass had little effect on preservation of functioning (4).

Transitions between various levels of physical function and disability in elderly subjects have been described (14–19). Beckett et al. (14) showed that the decline in mean level of physical function in their elderly subjects did not imply that all subjects followed a steady course of decline; some subjects recovered from disability even at the oldest ages. Anderson et al. (15) emphasized the heterogeneity of transitions between states of disability that can occur in elderly subjects and demonstrated the importance of the incorporation of knowledge about previous patterns of disability into estimations of the probability of subsequent transitions in disability status. Other studies (16–19) emphasize the prognostic importance of prior disability episodes on new episodes and the high rates of recovery from disability that older subjects experience. The implication of the later findings supports the argument that additional efforts could extend the recovery and independence of older subjects at high risk of recurring disability (17, 19).

The present investigation was undertaken to extend current understanding of transitions between states of functioning in the elderly within the context of the disablement model by the application of marginal structural models (MSMs) (20, 21). MSMS provide less biased estimates of the effects of interest in the presence of the time-dependent confounding inherent in the disablement model, and they permit more direct population-level inferences than can be derived from more conventional statistical approaches (4, 22). Application of statistical methods for causal inference provides the opportunity to unravel the complex causal associations in the disablement model to an extent not easily achieved or even possible with standard statistical methods.

MATERIALS AND METHODS

Study sample

Eligible subjects were 947 women and 708 men (n = 1,655) who were a subset of 2,092 men and women 55 years of age or older who resided in and around Sonoma, California, and who participated in a community-based, longitudinal study of the effect of aging on functioning in the elderly (23, 24). The protocols were approved by the Committee for the Protection of Human Subjects, University of California, Berkeley and the Committee for Human Research at the University of California, San Francisco. The 1,655 subjects were those for whom bioelectric impedance measurement, physical performance, and physical function data were available at the baseline evaluation (May 1993–December 1994). Full details of the protocol have been published previously (23–25). Data from the present analysis were derived from the baseline and three subsequent evaluations (September 1995–November 1996, June 1998–October 1999, and February 2000–March 2001). Complete data from all four evaluations and from the first three and the first two evaluations were available for 648, 884, and 1,236 subjects, respectively.

Assessment of functional limitation

Self-reported functional limitation was based on 10 questions (appendix 1) that assessed the degree of difficulty that a participant reported in various domains of physical function (upper- and lower-body domains of varying complexity) (3, 26–29). Participants who reported having “a lot of difficulty” doing one or more of the functions or not doing at least one because they were unable or were advised by a physician not to do so were classified as having self-reported limitation.

Measurement of body composition

Estimates of fat mass and lean mass were derived from resistance and reactance measured by bioelectric impedance (BIA101Q Quantum Body Composition Analyzer System; RJL Systems, Clinton Township, Michigan) based on study-specific validation equations (3). The total variances in lean mass accounted for by these regressions were 0.85 for men.
and 0.80 for women. Similar regressions were performed for lean plus bone mass. Fat mass (in kilograms) was obtained by the subtraction of lean plus bone mass from body weight. L/F was defined as the ratio of lean body mass to fat mass (both in kilograms). Measurements of appendicular fat-free mass were not available.

Measurement of LTPA

At each evaluation, subjects reported their average weekly participation over the past 12 months (average number of times per week for each activity) in 22 specific physical activities that spanned a wide range of energy expenditures (24). Each activity was assigned a metabolic equivalent (MET) value (1 MET = oxygen consumption of 3.5 ml/kg minute⁻¹) from a standard compendium of MET values (30). Two separate classifications of LTPA were created.

A continuous LTPA variable was derived based on a weighted sum of the frequency and MET values of the 22 activities for each subject: \( \sum_{i=1}^{22} (\text{no. of times/week} \times \text{METs/week}) \). On the basis of recommended levels of physical activity (31), we created a four-level categorical variable that corresponded to 1) no LTPA (0 METs/week); 2) insufficiently active (>0–22.5 METs/week, where 22.5 METs/week represents the minimum recommended level based on the MET value for brisk walking (4.5)); 3) meeting the minimum recommendation (>22.5–<35 METs/week); and 4) highly active (≥35 METs/week).

At baseline, subjects were asked whether their level of physical activity had changed in the preceding 5–10 years. Responses were recorded as a dichotomous variable (1 = report of any decline, 0 = no change or increase).

Other covariates

Weight and height were measured by using a standard protocol at each visit, and body mass index was calculated as weight in kilograms divided by height in meters squared. We categorized body mass index into three groups (<25, 25–<30, ≥30 kg/m²) (32, 33). At each survey, subjects were classified as having none, one, or more than one chronic disease based on the new or past occurrence of self-reported cancer, cardiovascular disease, cerebrovascular disease, diabetes mellitus, kidney disease, liver disease, or Parkinson’s disease. The presence of depression was based on a score of 16 or more on the Center for Epidemiologic Studies Depression Scale (34) and/or current use of an antidepressant medication (direct inspection of all medications was conducted at each interview). At each survey, smoking was classified as never, current, or former (24). Subjects rated their overall health (excellent, good, fair, or poor), which was summarized as a dichotomous variable: 0 = excellent/good, 1 = fair/poor). Living arrangements were defined for each subject as living alone, living with a spouse, or living with a nonspouse (35). Walking speed (feet per second; 1 foot = 0.3 m) was measured by the number of feet walked in 60 seconds (24).

Statistical analysis

Description. Functioning in the elderly was evaluated as a stochastic process (36) that changes over time. For example, \( Y(t) \in \{0, 1, \ldots, 4\} \) can be viewed as a discrete-time process during which a person might or might not exhibit signs \( \{Y(t) = 1, Y(t) = 0, 1 = \text{limitation}, 0 = \text{no limitation}\} \) associated with functional limitation at observation times \( t \). We can represent this stochastic process with a multinomial vector \( \mathbf{Y} = \mathbf{y} \left[ \begin{array}{c} Y(1) = y(1), \ Y(2) = y(2), \\ Y(3) = y(3), \ Y(4) = y(4) \end{array} \right] \). Thus, we can evaluate the process as different “histories” or “courses” of disablement (transitions) defined on an interval \((t = 1, \ldots, 4)\) and having a distribution, \( \Pr(\mathbf{Y} = \mathbf{y}) \), and state-space \( \Omega = 16 \) possible realizations (\( 2^4 \) combinations of impaired/not impaired over four time points). We are interested in how the distribution \( \Pr(\mathbf{Y} = \mathbf{y}) \) might vary given underlying factors that occur in the disablement process that can lead to different transitions, in particular, the marginal (unconditional) effects of L/F and LTPA.

We applied MSMs, as in previous studies (37–39), to evaluate the effects of exposure variables (e.g., L/F, LTPA) in the presence of time-dependent confounders (e.g., walking speed, health status) that are affected by previous levels of the exposure variables. Standard approaches, under these circumstances, would yield biased estimates of the effects (40). The covariates described above are assumed to represent all of the measurable confounders of LTPA and L/F. In the MSM framework, we control for the effects of these confounders relative to L/F and LTPA through time-specific exposure (“treatment”) models. In addition, we can control for selection bias from various sources of loss to follow-up by the use of censoring models at each time point. From these respective models, we obtain subject-specific, time-specific weights (20), which can be applied in an MSM to obtain unbiased estimates of the marginal effects of L/F and LTPA.

Application of the MSM. MSMs are based on the concept of counterfactual variables. An exposure-specific counterfactual (potential outcome) variable is a random variable that represents a subject’s set of outcomes had the subject, contrary to fact, had an exposure history other than the one actually observed (20). Formal presentation of the theory, assumptions, and applications of MSMs toward epidemiologic research has been reported extensively (4, 20–22, 38–41). A formal data analysis that assessed the marginal effects of L/F and LTPA on functional limitation is available (4). We have listed the restrictions/assumptions required to identify causal effects with MSMs in appendix 2.

We assume a generalized MSM for the marginal distribution of \( \mathbf{Y}_d \):

\[
\Pr(\mathbf{Y}_d = \mathbf{y}) = m(\mathbf{y} | \beta).
\]

\( \mathbf{Y}_d \) is defined as the multivariate vector that represents different transitions, or histories of functioning, if, contrary to fact, subjects had followed joint exposure history \( \bar{a} = (\text{LTPA}, L/F) \rightarrow (\text{LTPA}(0), L/F(0), \ldots, \text{LTPA}(t), L/F(t)) \).

We assume that \( \mathbf{Y}_d \) has a joint probability distribution:

\[
\Pr(\mathbf{Y}_d = \mathbf{y}) = \Pr(\mathbf{Y}_d(1) = y(1), \mathbf{Y}_d(2) = y(2), \mathbf{Y}_d(3) = y(3), \mathbf{Y}_d(4) = y(4)).
\]

To formulate the MSM model, we factorize \( \Pr(\mathbf{Y}_d = \mathbf{y}) \) as the product.
\[
\prod_{t=1}^{4} \Pr(Y_a(t) = y(t) | \bar{Y}_a(t-1) = \bar{y}(t-1)).
\]

We model each term \( \Pr(Y_a(t) | \bar{Y}_a(t-1)) \) of the product separately at each \( t \), where we assume a logistic MSM that evaluates the exposure-specific mean functional limitation as a linear combination of \( L/F \) and LTPA history, \( \bar{a} \), through \( t \) within strata of past functional history \( \bar{y}(t-1) \):

\[
\text{Logit} \Pr(Y_a(t) = 1 | \bar{Y}_a(t-1) = \bar{y}(t-1)) = \beta_{0i} + \beta_{1i} \times \bar{a}(t) + \beta_{2i} \times \bar{y}(t-1).
\]

(Rer refer to appendix 3 for the exact formulation of \( \bar{a}(t) \) and \( \bar{y}(t-1) \) used in the models. Note that when \( t = 1, \bar{y}(t-1) \) is an empty set.) Evaluation of the effects of LTPA and \( L/F \) on \( Y_a \) is based on the assumption that, for any given \( t \), LTPA affects \( L/F \), and both of these affect \( Y \); \( LTPA \) is based on average activity levels reported by a subject over the 12 months prior to \( t \), \( L/F \) is measured approximately at \( t \), and \( Y \) is a measure of the functional limitation reported by a subject for the month prior to \( t \). Given that the observed changes in \( L/F \) over the study period were small, we assume that any differences in \( L/F \) between the period in which \( L/F \) affects \( Y(t) \) and \( L/F \) is measured at \( t \) are negligible. The parameters (\( \beta_{1i}, \beta_{2i} \)) have direct interpretation and are not reported; rather, we use these parameters, as described in the next section, to construct the distribution of interest \( \Pr(Y_a = \bar{y}) \).

The parameters are estimated by the solution of the inverse probability of treatment weight and the inverse probability of censoring weight estimating equations (20). Solution of these estimating equations is equivalent to a weighted regression with \( y(t) \) as a function of \( \bar{a}(t) \) and \( \bar{y}(t-1) \), with logit link and subject-specific, time-specific weights. A general discussion of the calculation of subject-specific weights can be found (20, 21), and a practical example of applying subject-specific weights in a previous analysis using MSMs is available (4).

Regressions were implemented with standard logistic regression software (PROC LOGISTIC, SAS version 8.2; SAS Institute, Inc., Cary, North Carolina) with weights.

**Computation of counterfactual transition distributions.** To compute the distribution of transitions in functioning, \( \Pr(Y_a = \bar{y}) \), for a counterfactual exposure history, \( \bar{a} = (LTPA, L/F) \), we first estimate the marginal distributions of functional status \( \Pr(Y_a(t) = y(t) | \bar{Y}_a(t-1) = \bar{y}(t-1)) \) for each time \( t \) based on the time-specific parameter estimates \( \beta_{1i}, \beta_{2i} \). Second, we compute the product of these marginal distributions of functional status from \( t = 1, \ldots, 4 \):

\[
\prod_{t=1}^{4} \Pr(Y_a(t) = y(t) | \bar{Y}_a(t-1) = \bar{y}(t-1)).
\]

An explicit example of this computation is given in appendix 4.

Confidence intervals (95 percent) for each transition probability were calculated with the standard error based on a bootstrap distribution of 1,000 estimates for each of the different transitions. If the distributions were not normal, the 2.5 and 97.5 percentiles of the distribution were selected (42).

**RESULTS**

Baseline characteristics of the study population are displayed in table 1. The median duration of follow-up for both women and men was approximately 6.4 years (interquartile range: 5.6–6.9). The median number of activities for which subjects reported difficulty was 2.0 (interquartile range: 1–4 for women, 1–3 for men); the three most frequently reported activities were 1) getting up from a stooping, crouching, or kneeling position; 2) stooping, crouching, or kneeling; and 3) lifting or carrying items over 10 pounds (4.54 kg) (women) and standing in place for 15 minutes or longer (men).

Tables 2 and 3 present proportions of transitions that represent the onset of functional limitation without recovery in women and men, respectively, along with five of the possible counterfactual joint exposure histories for \( L/F \) and LTPA. The proportions of transitions based on the observed data (column 3) represent the counterfactual distribution actually observed in the study population. Fifty percent of women and 71 percent of men did not report any limitation over the entire study period. At all four surveys, approximately 9 percent of women and 2.4 percent of men reported limitation in at least one function. Onset of functional decline without recovery (summation of the proportions of the other transitions in tables 2 and 3) was observed for 16.3 percent of women and 9.3 percent of men. Table 4 presents proportions of transitions that represent full recovery from a baseline limitation and other transitions that represent temporal (nonmonotonic) patterns of limitation and recovery over time. Approximately 5 percent of women and 3.4 percent of men experienced full recovery from baseline limitation (rows 1–2, column 3), whereas 14 percent of women and 11.7 percent of men experienced a new limitation followed by recovery (rows 3–4, column 3).

The proportions of all possible transitions are redistributed if the study population, contrary to fact, experienced the selected counterfactual exposure histories (tables 2–4, columns 4–8). For example, we observe a general increase in risk of functional impairment in the subjects if they did not exercise over the study period but maintained the same levels of \( L/F \) (tables 2–4, column 4). The proportion of women without any limitation during the study (table 2, row 1) drops from 50 percent to 38.4 percent, while the proportion who are limited at all time points rises from approximately 9 percent to 15.3 percent. A similar pattern occurs for the men. Proportions of transitions suggestive of functional limitation were not greater in all cases and were not statistically different from the proportions actually observed in the data (column 3).

If, contrary to fact, subjects reported at all surveys that they exercised at high aerobic levels (≥35 METs/week), the likely onset of functional limitation without recovery would be expected to decrease (tables 2 and 3, column 5). We observed a reduction of 53 percent (7.4 → 3.5 percent) in women’s chances of developing a functional limitation at the last survey compared with their actual observed history (table 2, row 2, column 5 vs. column 3). Furthermore, high, sustained levels of aerobic exercise play a role in the delay of the onset of functional limitation (table 2, rows 3 and 4). For example, the risk for women who experience functional
<table>
<thead>
<tr>
<th>Variable*</th>
<th>Body composition data available (n = 1,655)$\dagger$</th>
<th>Body composition data not available (n = 437)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69.0 (56–84) 69.5 (56–82)</td>
<td>75.0 (56–89) 75.0 (56–89)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.5 (20.3–34.8) 26.8 (22.0–34.4)</td>
<td>25.8 (19.2–35.6) 26.6 (21.2–37.7)</td>
</tr>
<tr>
<td>Lean body mass:fat mass ratio</td>
<td>1.45 (0.98–2.45) 2.6 (1.9–4.2)</td>
<td>Not measured Not measured</td>
</tr>
<tr>
<td>Walking speed (feet/second)</td>
<td>2.3 (1.3–3.0) 2.3 (1.5–3.0)</td>
<td>2.0 (1.0–2.8) 1.8 (1.2–2.8)</td>
</tr>
<tr>
<td>METs§/week of physical activity (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6.6 3.7</td>
<td>20.7 15.2</td>
</tr>
<tr>
<td>&gt;0–22.5</td>
<td>22.8 18.8</td>
<td>20.7 18.1</td>
</tr>
<tr>
<td>&gt;22.5–&lt;35</td>
<td>20.0 14.4</td>
<td>15.7 21.7</td>
</tr>
<tr>
<td>≥35</td>
<td>50.4 63.1</td>
<td>38.5 43.5</td>
</tr>
<tr>
<td>Missing</td>
<td>0.2 0.1</td>
<td>4.3 1.4</td>
</tr>
<tr>
<td>Chronic health condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>57.6 53.2</td>
<td>44.6 38.4</td>
</tr>
<tr>
<td>Yes</td>
<td>42.4 46.8</td>
<td>55.4 61.6</td>
</tr>
<tr>
<td>Depression¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>81.0 90.2</td>
<td>11.0 6.5</td>
</tr>
<tr>
<td>Yes</td>
<td>15.0 6.4</td>
<td>73.6 76.8</td>
</tr>
<tr>
<td>Missing</td>
<td>4.0 3.4</td>
<td>15.4 16.7</td>
</tr>
<tr>
<td>Decline in physical activity prior to baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>62.8 66.6</td>
<td>44.5 44.9</td>
</tr>
<tr>
<td>Decline</td>
<td>36.7 33.2</td>
<td>54.8 55.1</td>
</tr>
<tr>
<td>Missing</td>
<td>0.4 0.3</td>
<td>0.7 0.7</td>
</tr>
<tr>
<td>Living arrangements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lives alone</td>
<td>39.7 11.6</td>
<td>46.0 15.2</td>
</tr>
<tr>
<td>Lives with spouse</td>
<td>53.1 83.6</td>
<td>40.6 79.0</td>
</tr>
<tr>
<td>Lives with nonspouse</td>
<td>7.2 4.8</td>
<td>13.4 5.8</td>
</tr>
<tr>
<td>Smoking history# (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>48.9 33.6</td>
<td>49.5 29.0</td>
</tr>
<tr>
<td>Current</td>
<td>8.7 6.5</td>
<td>10.0 10.9</td>
</tr>
<tr>
<td>Former</td>
<td>42.4 59.9</td>
<td>40.5 60.1</td>
</tr>
<tr>
<td>Self-rated health (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent/ good</td>
<td>86.1 84.6</td>
<td>68.4 64.5</td>
</tr>
<tr>
<td>Fair/poor</td>
<td>13.6 15.4</td>
<td>30.6 34.8</td>
</tr>
<tr>
<td>Missing</td>
<td>0.3 0.1</td>
<td>0.9 0.7</td>
</tr>
<tr>
<td>Self-reported functional limitation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>70.9 84.7</td>
<td>50.7 58.7</td>
</tr>
<tr>
<td>Any</td>
<td>29.1 15.3</td>
<td>49.3 41.3</td>
</tr>
<tr>
<td>ADL§ abnormality# (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>97.7 98.7</td>
<td>82.2 80.4</td>
</tr>
<tr>
<td>Any</td>
<td>2.3 1.3</td>
<td>17.8 17.4</td>
</tr>
<tr>
<td>Missing</td>
<td>2.2</td>
<td></td>
</tr>
</tbody>
</table>

* All continuous variables are expressed as median (5th–95th percentiles).
† Baseline information from 104 subjects could not be used because data on one or more covariates were missing.
‡ One foot = 0.3 m.
§ METs, metabolic equivalents; ADL, activities of daily living.
¶ Based on Center for Epidemiologic Studies Depression Scale score and use of antidepressant medication.
# Not included in treatment or censoring models because of a lack of association with the outcome (smoking) or the numbers were too small (ADL abnormality).
### TABLE 2. Proportions of selected transitions for onset of functional limitation over surveys 1–4 for observed data and several counterfactual scenarios for women in the Study of Physical Performance and Age-Related Changes, Sonoma, California, 1994–2000

<table>
<thead>
<tr>
<th>Transitions of functional limitation (yes = 1, no = 0)</th>
<th>Observed data (S1–S4)</th>
<th>No.</th>
<th>Median L/F, high LTPA</th>
<th>Median L/F, no LTPA</th>
<th>1 unit over median L/F, no LTPA</th>
<th>Increasing LTPA and L/F</th>
<th>Decreasing LTPA and L/F</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 0 0 0</td>
<td>192</td>
<td>0.505</td>
<td>0.384</td>
<td>0.490</td>
<td>0.639</td>
<td>0.481</td>
<td>0.310</td>
</tr>
<tr>
<td>0 0 0 1</td>
<td>28</td>
<td>0.074</td>
<td>0.127</td>
<td>0.035</td>
<td>0.101</td>
<td>0.039</td>
<td>0.129</td>
</tr>
<tr>
<td>0 0 1 1</td>
<td>16</td>
<td>0.042</td>
<td>0.063</td>
<td>0.023</td>
<td>0.021</td>
<td>0.016</td>
<td>0.107</td>
</tr>
<tr>
<td>0 1 1 1</td>
<td>18</td>
<td>0.047</td>
<td>0.038</td>
<td>0.029</td>
<td>0.012</td>
<td>0.026</td>
<td>0.053</td>
</tr>
<tr>
<td>1 1 1 1</td>
<td>33</td>
<td>0.087</td>
<td>0.153</td>
<td>0.131</td>
<td>0.030</td>
<td>0.134</td>
<td>0.172</td>
</tr>
</tbody>
</table>

* Proportions of transitions are based on the distribution (i.e., frequencies) of occurrence in the observed data. In fact, the “Observed” category is one of the set of all possible counterfactual exposure histories. Proportions of transitions, under other counterfactual exposure histories, were computed based on estimates from marginal structural models.

† S, survey; L/F, ratio of lean body mass to fat mass; LTPA, leisure-time physical activity.

‡ Starting with the lowest LTPA category at baseline, there is a one-unit increase in LTPA category with each successive survey. In conjunction with this increase in LTPA is a lag increase in L/F over the population median level (0.2, 0.5) at time = 3, 4.

§ Beginning with the highest LTPA category at baseline, there is a one-unit decrease in LTPA category with each successive survey. There is a lag decrease in L/F below the population median (–0.2, –0.5) at time = 3, 4.

¶ 95% confidence intervals (values separated by commas) that overlap across different exposure histories for given transitions indicate no statistical difference at the alpha 0.05 level. Confidence intervals were derived from the standard error of a distribution of 1,000 bootstrap estimates for each transition probability.

### TABLE 3. Proportions of selected transitions for onset of functional limitation over surveys 1–4 for observed data and several counterfactual scenarios for men in the Study of Physical Performance and Age-Related Changes, Sonoma, California, 1994–2000

<table>
<thead>
<tr>
<th>Transitions of functional limitation (yes = 1, no = 0)</th>
<th>Observed data (S1–S4)</th>
<th>No.</th>
<th>Median L/F, high LTPA</th>
<th>Median L/F, no LTPA</th>
<th>1 unit over median L/F, no LTPA</th>
<th>Increasing LTPA and L/F</th>
<th>Decreasing LTPA and L/F</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 0 0 0</td>
<td>206</td>
<td>0.708</td>
<td>0.589</td>
<td>0.622</td>
<td>0.730</td>
<td>0.635</td>
<td>0.563</td>
</tr>
<tr>
<td>0 0 0 1</td>
<td>11</td>
<td>0.038</td>
<td>0.033</td>
<td>0.024</td>
<td>0.015</td>
<td>0.014</td>
<td>0.053</td>
</tr>
<tr>
<td>0 0 1 1</td>
<td>11</td>
<td>0.038</td>
<td>0.008, 0.089</td>
<td>0.004, 0.044</td>
<td>0.003, 0.046</td>
<td>0.001, 0.027</td>
<td>0.010, 0.157</td>
</tr>
<tr>
<td>0 1 1 1</td>
<td>5</td>
<td>0.017</td>
<td>0.046</td>
<td>0.042</td>
<td>0.014</td>
<td>0.025</td>
<td>0.083</td>
</tr>
<tr>
<td>1 1 1 1</td>
<td>7</td>
<td>0.024</td>
<td>0.004, 0.088</td>
<td>0.007, 0.058</td>
<td>0.006, 0.065</td>
<td>0.005, 0.071</td>
<td>0.008, 0.095</td>
</tr>
</tbody>
</table>

* Proportions of transitions are based on the distribution (i.e., frequencies) of occurrence in the observed data. In fact, the “Observed” category is one of the set of all possible counterfactual exposure histories. Proportions of transitions, under other counterfactual exposure histories, were computed based on estimates from marginal structural models.

† S, survey; L/F, ratio of lean body mass to fat mass; LTPA, leisure-time physical activity.

‡ Starting with the lowest LTPA category at baseline, there is a one-unit increase in LTPA category with each successive survey. In conjunction with this increase in LTPA is a lag increase in L/F over the population median level (0.2, 0.5) at time = 3, 4.

§ Beginning with the highest LTPA category at baseline, there is a one-unit decrease in LTPA category with each successive survey. There is a lag decrease in L/F below the population median (–0.2, –0.5) at time = 3, 4.

¶ 95% confidence intervals (values separated by commas) that overlap across different exposure histories for given transitions indicate no statistical difference at the alpha 0.05 level. Confidence intervals were derived from the standard error of a distribution of 1,000 bootstrap estimates for each transition probability.
TABLE 4. Proportions summed for selected groups of transitions* over surveys 1–4 for observed data and counterfactual scenarios for women and men in the Study of Physical Performance and Age-Related Changes, Sonoma, California, 1994–2000

<table>
<thead>
<tr>
<th>Transitions of functional limitation (yes = 1, no = 0)</th>
<th>No.</th>
<th>Observed data (S1–S4)</th>
<th>Selected counterfactual exposure histories of L/F† and LTPA† (S1–S4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median L/F, no LTPA</td>
</tr>
<tr>
<td>Onset of functional recovery (1\rightarrow0) transitions‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>18</td>
<td>0.048</td>
<td>0.032</td>
</tr>
<tr>
<td>Men</td>
<td>10</td>
<td>0.034</td>
<td>0.048</td>
</tr>
</tbody>
</table>

| Temporal functional limitation transitions§ |     |                      |                     |                      |                                 |                     |                      |
| Women                           | 53  | 0.139                | 0.072              | 0.147               | 0.063               | 0.121              | 0.076               |
| Men                             | 34  | 0.117                | 0.118              | 0.139               | 0.114               | 0.165              | 0.083               |

| Temporal functional recovery transitions¶ |     |                      |                     |                      |                                 |                     |                      |
| Women only                       | 22  | 0.058                | 0.132              | 0.076               | 0.073               | 0.104              | 0.120               |
|                                  |     |                      | 0.071              | 0.193               | 0.042              | 0.110              | 0.028              | 0.057              | 0.183               |

* Particular transitions were grouped and their respective estimated proportions were summed given the characteristics of the transitions and/or infrequency with which they occurred in the sample.
† S, survey; L/F, ratio of lean body mass to fat mass; LTPA, leisure-time physical activity.
‡ Transitions for women: 1\rightarrow1\rightarrow1\rightarrow0 (n = 26), 0\rightarrow1\rightarrow0\rightarrow0 (n = 14), 1\rightarrow0\rightarrow1\rightarrow1 (n = 6), 0\rightarrow1\rightarrow1\rightarrow0 (n = 7); transitions for men: 0\rightarrow0\rightarrow1\rightarrow0 (n = 5). For men, a similar comparison of these two exposure histories suggests a further reduced risk of functional limitation when L/F levels increase with increasing exercise over time (table 3, column 7 vs. column 5). In the counterfactual world where the population experienced a faster rate of decline in physical activity (column 8) and, consequently, a lower L/F, the risk of functional decline would be as large as that if they did not exercise at all.

We also examined the distribution of functioning over time if subjects were not physically active but if, contrary to fact, their L/F was one unit greater than their observed L/F (column 6). The effects appear to vary somewhat for men and women. For women (table 2), we observed an increase in the proportion of subjects without functional limitation (row 1, column 3 vs. column 6) and women who experienced delayed functional limitation (row 2, column 7) throughout the study. For men, a similar comparison of these two exposure histories suggests a further reduced risk of functional limitation when L/F levels increase with increasing exercise over time (table 3, column 7 vs. column 5). In the counterfactual world where the population experienced a faster rate of decline in their physical activity (column 8) and, consequently, a lower L/F, the risk of functional decline would be as large as that if they did not exercise at all.
DISCUSSION

In a population of elderly subjects, we characterized dis-
ability as different transitions in functional change over
time. On the basis of MSM methodology, we estimated the
differences in the occurrence of these transitions if the study
population sustained patterns of L/F and LTPA different
from those it actually experienced. Estimation of differences
in functioning under these conditions based on standard
statistical methods would not have been possible.

The results suggest that L/F and LTPA affect function-
ing differently. L/F, which varied minimally with time, ap-
peared to establish levels (strata) of functioning at an early
stage of the disablement process that continued over time.
For example, we observed that if the population’s L/F was
one unit greater, the result was a smaller proportion of sub-
jects who experienced limitation at all four surveys and a
larger proportion of those who were limitation free over
the same period. By contrast, high, sustained levels of LTPA
did not increase the proportion of subjects without limitation
nor reduce the proportion with a limitation at all four sur-
veys. In fact, in the latter case, the proportion of subjects
who were functionally limited at all four surveys increased.
However, we observed that high levels of LTPA reduced the
risk of onset of functional limitation in subjects without past
limitation and increased the probability of recovery of func-
tioning for those who were previously limited. On the basis
of these findings, we conclude that LTPA reduces the risk
of future functional limitation conditional on the level of func-
tioning conferred by L/F.

The data also suggest that the beneficial effects of LTPA
with respect to functioning occur indirectly through an in-
crease in L/F (i.e., a reduction in the amount of fat relative
to lean mass). We did not investigate the potential role of
past physical activity history on baseline levels of L/F. There
was also a suggestion of a direct effect of LTPA possibly on
some component of functioning (i.e., improved mobility/
dexterity). For example, among women, higher levels of
physical activity, even without an increase in L/F, reduced
the onset of functional limitation (table 2, column 4 vs.
column 7). A comparison of the effects in men suggested
that the advantages conferred by LTPA occur indirectly
through L/F. The results were consistent with a previous
analysis that indicated that LTPA exerts its beneficial effects
through reductions in fat mass relative to lean body mass (4).

One potential limitation of the study could have arisen
from failure to satisfy the assumptions required to obtain
unbiased MSM estimates. For example, we may not have
controlled for all measurable confounders of LTPA and L/F
and/or misspecified the treatment and censoring models
that were used. We approximated these assumptions by thor-
oughly examining the potential confounders in our data and
developing treatment/censoring models to control for the ef-
fects of confounding and selection bias. We assume that we
met all other assumptions required to implement the MSM.

We chose to examine the causal effect of L/F with respect
to functioning. However, to investigate causal effects, the
counterfactual outcomes under different levels of the expo-
sure variable must be well defined. Different processes
could have given rise to the same L/F (e.g., exercise, diet),
and these different processes could have different implica-
tions for the outcome that corresponds to the given L/F. For
our purposes, we defined L/F as a summary endpoint of
these different processes, which in itself has ramifications
for functioning regardless of the processes that lead to L/F.
Evaluation of the differential effects of L/F on functioning
with respect to these different processes was possible but
was not a goal of this analysis.

In summary, our data provide population-level estimates
of the extent to which functional limitation can vary over
time in the elderly and the potential causal roles of physical
activity and body composition in this variation. These causal
estimates go beyond what can be inferred from studies that
have used more conventional methods of analysis. In addi-
tion, our observations point to the need to account for this
temporal variation in functioning when evaluating any in-
terventions designed to improve the functional status in the
elderly. Failure to consider this inherent variability could
lead to overestimation of the impacts of interventions and
their likely public health significance.

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In lifting or carrying items over 10 pounds, like a bag of groceries?
In standing in place for 15 minutes or longer?
In sitting for long periods, say, 1 hour?
In standing up after sitting in a chair?
In walking alone up and down a flight of stairs?
In walking two to three neighborhood blocks?

Response categories:
A lot of difficulty
Some difficulty
A little difficulty
No difficulty
Don’t do on a doctor’s orders
Don’t do because unable
Never do the activity

APPENDIX 2

Assumptions Underlying MSM Implementation

In general terms, we are required to apply the following restrictions/assumptions to identify causal effects with MSMs: 1) counterfactual outcomes exist and are well defined for each exposure history that a subject could experience other than the one observed; 2) consistency assumption—observed data are just one realization of the “full” counterfactual data; 3) we denote the temporal ordering of the data as \((L(1), A(1), Y(1), \ldots, L(4), A(4), Y(4))\), that is, the occurrence of covariates \(L\) and exposure \(A\) precede outcome \(Y\) in the causal pathway, and the \(L\) influence the exposure \(A\); 4) no unmeasured confounding, or sequential randomization assumption—exposure process (e.g., LTPA, L/F) over time, conditional on the past exposure and other covariates, is independent of the counterfactual outcome and is not predictive of what treatment will be received in the future; 5) experimental treatment assignment—all possible treatments, conditional on past treatment, are observed for given covariates; 6) no selection bias exists, given the measured covariates (i.e., data missing at random or no informative censoring given the measured covariates); and 7) there is no model misspecification (i.e., models for treatment, censoring, and outcome (MSM) models).

APPENDIX 3

Exposure History Defined in the MSM Analysis

In the women’s analysis, we define joint exposure history \(\tilde{a}\) as a function \((L/F(t) + \text{LTPA}(t) + \text{LTPA}(t-1))\), where \(L/F(t)\) represents the “running” mean of L/F through time \(t\), LTPA(t) consists of four levels of exercise pattern at time \(t\) (categorical form), and \(\text{LTPA}(t-1)\) consists of three levels (collapsed first and second levels) based on a categorization of the “running” mean of LTPA through time \(t\). These functions were chosen based on a model selection process that compared different MSMs by using different functions of L/F and LTPA history. \(Y(t-1)\) represents a vector of separate terms of previous functional history that were included in the models, for example, \(Y(1)\) for the model at \(t = 2\); \((Y(1), Y(2))\) at \(t = 3\); and \((Y(1), Y(2), Y(3))\) at \(t = 4\).

APPENDIX 4

Computation of Counterfactual Transition Distributions

We illustrate the method by which we compute the distribution of transitional patterns \(Pr(Y_{a} = \tilde{y})\) for a counterfactual exposure history \(\tilde{a}\). At each \(t = 1, \ldots, 4\), we estimate \(Pr(Y_{a}(t) = 1|\tilde{Y}_{a}(t-1))\) with the parameter estimates from the following model at each \(t\):

\[
\text{Logit} \Pr(Y_{a}(t) = 1|\tilde{Y}_{a}(t-1)) = \beta_{0} + \beta_{1} \times \tilde{a}(t) + \beta_{2} \times \tilde{y}(t-1),
\]

where \(\tilde{a}(t)\) represents exposure history described in appendix 3; \(\beta_{1}\) corresponds to a vector of beta coefficients associated with the components of \(\tilde{a}(t)\); \(\tilde{y}(t-1)\) represents past functional history to \(t\), which is a vector that cumulates individual terms of past functional limitation status over time; and \(\beta_{2}\) represents the vector of beta coefficients corresponding to those terms of past functional limitation.

We estimate the marginal probability of functional limitation \(= 1\) at \(t = 1\)

\[
Pr(Y_{a}(1) = 1) = \expit(\beta_{0} + \beta_{11})
\]

and its complement, the probability of functional limitation \(= 0\), as

\[
1 - Pr(Y_{a}(1) = 1) = 1 - \expit(\beta_{0} + \beta_{11}).
\]

We estimate the marginal probability of functional limitation \(= 1\) at \(t = 2\) within strata of past functional history as

\[
Pr(Y_{a}(2) = 1|T_{a}(1) = 0) = \expit(\beta_{02} + \beta_{12})
\]

\[
Pr(Y_{a}(2) = 1|T_{a}(1) = 1) = \expit(\beta_{02} + \beta_{12} + \beta_{22})
\]

and the marginal probability of functional limitation \(= 0\) as

\[
1 - Pr(Y_{a}(2) = 1|T_{a}(1) = 0) = 1 - \expit(\beta_{02} + \beta_{12})
\]

\[
1 - Pr(Y_{a}(2) = 1|T_{a}(1) = 1) = 1 - \expit(\beta_{02} + \beta_{12} + \beta_{22}).
\]

(Note that, for convenience, we use the same fitted parameter estimates above \(\beta_{02}, \beta_{12}\) to illustrate two different models \(Pr(Y_{a}(2) = 1|T_{a}(1) = 0)\) and \(Pr(Y_{a}(2) = 1|T_{a}(1) = 1)\); the parameter estimates \(\beta_{02}, \beta_{12}\) indeed are different each time we add terms to the models. A similar pattern occurs below for \(t = 3\) and \(t = 4\)).

For \(t = 3\), the marginal probability of functional limitation \(= 1\) (marginal probability of functional limitation \(= 0\)

not shown) within strata of functional history is given by

\[
\Pr(Y_4(t) = 1 | Y_{a}(2) = (y(1) = 0, y(2) = 0)) = \exp(it(\hat{\beta}_{03} + \hat{\beta}_{13})
\]

\[
Pr(Y_4(t) = 1 | Y_{a}(2) = (y(1) = 1, y(2) = 0)) = \exp(it(\hat{\beta}_{03} + \hat{\beta}_{13} + \hat{\beta}_{231})
\]

\[
Pr(Y_4(t) = 1 | Y_{a}(2) = (y(1) = 0, y(2) = 1)) = \exp(it(\hat{\beta}_{03} + \hat{\beta}_{13} + \hat{\beta}_{231})
\]

\[
Pr(Y_4(t) = 1 | Y_{a}(2) = (y(1) = 1, y(2) = 1)) = \exp(it(\hat{\beta}_{03} + \hat{\beta}_{13} + \hat{\beta}_{231} + \hat{\beta}_{233})
\]

Equations to estimate the probability of functional limitation = 1 for \( t = 4 \) build on the pattern for \( t = 3 \), except eight equations are estimated for each of the eight strata of past functional history.

We can now construct the joint probability of functional limitation over time by using the cumulative product of computed probabilities from above,

\[
\prod_{t=1}^{4} \Pr(Y_a(t) = y(t) | Y_a(t-1) = y(t-1)),
\]

to obtain the marginal distribution of transitions for exposure history \( a \) for the entire duration of the study \( \Pr(Y_a = \bar{y}) \).