The Older the Better:
Are Elderly Study Participants More Nonrepresentative?

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The Older the Better:

Are Elderly Study Participants More Nonrepresentative?

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Running Title: Golomb 2012 - Elderly Nonrepresentative

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Abstract 247

Objective: Study subjects can differ from the target population they are taken to represent. We sought to investigate whether age modifies such differences.

Design: Cross-sectional examination of the relation of age to reported “relative activity” (compared to others of the same age), a bidirectionally-correlated proxy for relative vitality, in exemplars of randomized and observational studies.

Setting: University of California, San Diego (UCSD)

Participants: 2,404 adults age 40-79 including employees of UCSD, and their partners (San Diego Population Study, observational study). 1,016 adults not on lipid medications and without known heart disease, diabetes, cancer or HIV (UCSD Statin Study, randomized trial).

Measurements: Self-rated activity relative to others one’s age, 5-point Likert Scale, was evaluated by age decade; and related via correlation and regression to a suite of health-relevant subjective and objective outcomes.

Results: Successively older participants reported successively greater activity relative to others their age (greater departure from the norm for their age), p<0.001 in both studies. Relative activity significantly predicted (in regression adjusted for age) actual activity (times/week exercised); and numerous self-rated and objective health-predictors. These included general self-rated health, CES-D (depression score), sleep, tiredness, energy; body mass index, waist circumference, serum glucose, HDL-cholesterol, triglycerides, and white blood cell count. Indeed some health-predictor associations with age in participants were “paradoxical,” consistent with greater apparent health in older age – for study participants.

Conclusion: Study participants may not be representative of the population they are intended to reflect. Our results suggest that departures from representativeness may be amplified with increasing subject age.

Trial Registration: UCSD Statin Study – Clinicaltrials.gov # NCT00330980

(http://ClinicalTrials.gov)

Keywords: elderly; representativeness; sample selection; generalizability

Abbreviations: UCSD – University of California, San Diego

What this paper adds:

Section 1 – What is already known about the subject?

Study participants differ from the general population they are taken to represent and may be healthier.

Section 2 – What this study adds

This study demonstrated that with increasing age, self-selected study participants diverge increasingly from the population they are taken to represent. This has implications for studies of, and including, elderly subjects; affecting generalizability to older real-world populations.

Introduction

Relevance of data from human research studies to the general population depends on the similarity of study participants to those they are taken to represent, i.e. the “target” population. It is recognized that study samples may differ from the target population[1 2]. Often the study sample directly or disproportionately excludes the elderly[3-5] who have worse health and higher expected mortality[6], and who may differ from younger subjects in treatment effects.

Although there has been increasing emphasis (at least in principle) on inclusion of the elderly in studies[7], there are reasons for concern that elderly study participants may be less representative of their age group than younger subjects.

Self-selection by subjects themselves of a relatively healthier and more functional study population may occur in all ages[8-11], since even morbidity not requiring exclusion may nonetheless inhibit participation[1]. But since health problems and functional limitations that lead to self-exclusion may increasingly affect those older in age, we theorized that older age participants might be progressively less representative in indices relevant to function and vitality. Direct comparison of consenting participants to nonparticipants is problematic, since inherently the researcher has access only to the former group. Subjects’ ratings of themselves relative to others their age provides a tentative approach to evaluate whether departures rise with age, if such relative measures can be validated against direct measures.

We validated relative-activity, compared to other individuals ones age, against an activity metric that is absolute (vs relative); and assessed its relation to health-relevant outcomes. We examined reported relative-activity, compared to other individuals ones age, from available exemplars of two types of medical studies (observational and randomized controlled trial) to evaluate whether reported departure from normative function rises with increasing participant age.

Methods

Randomized Controlled Trial Subjects:

1,016 male and female subjects age 20-85 from the San Diego area were enrolled in the UCSD Statin Study, a double-blind, randomized, placebo-controlled trial assessing effects of statin cholesterol-lowering drugs on a relatively broadly sampled group of adults (a primary prevention sample). There was no imposed upper age limit. Subjects were men over age 20 and nonprocreative women not on lipid medications and without extremes of LDL-cholesterol (high or low), diagnosed cardiovascular disease, diabetes or HIV. More information on study population and design is available elsewhere[12].

Observational Study Subjects:

2,404 selected men and women ages 40-79 were enrolled in the San Diego Population Study, a population-based observational study identifying prevalence of arterial and venous disease. Subjects were drawn from current and former employees of the University of California San Diego (**UCSD**), as well as their spouses/ significant others – inclusion of which modestly extended the age range of participants in both directions[13]. In addition, a small number of non-UCSD volunteers were included. Subjects represented a spectrum of socioeconomic status, including unemployed and retired as well as working persons. A full description of the study population is available elsewhere[13].

Both studies were approved by the UCSD Human Research Protections Program, and all subjects gave informed consent to participate.

Relative Activity variable:

In both studies, “activity relative to others your age” was queried at baseline and measured on a 5-point Likert scale (1=much less active, 2=somewhat less active, 3=about as active, 4=somewhat more active, 5=much more active). Single-item self-rated assessments have shown strong predictive validity[14-16].

Validation Variables:

Other measures used: From the randomized trial, several other variables were chosen against which to validate the relative activity variable.

Absolute activity: We validated the relation of this relative activity measure to self-reported actual exercise frequency (number of episodes of vigorous exercise for at least 20 minutes over a week).

Health Predictor Variables: Self-rated and questionnaire variables known to predict mortality and health outcomes that were considered against relative activity included depressed mood (Center for Epidemiological Studies – Depression Scale aka CES-D, and self-rated), and single-item self-ratings of energy, tiredness, muscle weakness, fatigue with exertion, overall health, and satisfaction with health. Objective measures included platelet count (acute phase reactant), white blood count, serum glucose, HDL-cholesterol, triglycerides, body mass index (BMI), and waist circumference.

Analyses:

Activity associations and health implications of the relative activity measure were examined in older study participants (age > 50) from the randomized trial sample (in which these health variables were assessed), using correlation; and also regression analysis. In the latter, age-relative activity was the independent variable, and assessments were adjusted for actual age. For both study samples, we conducted bivariate analyses examining reported relative activity level as a function of age decade. This was followed by multivariable regression using ordinal logit with robust standard errors (aka White standard errors)[17] controlling for sex, ethnicity (categorical variable) and education (scaled from 1=grade school or less to 9=doctoral degree). All analyses were conducted using Stata™ version 8.0; StataCorp, College Station, Texas. Two-sided P-values less than 0.05 were designated statistically significant.

Results

Self-reported activity relative to others ones age related strongly to actual activity: (unadjusted) correlation 0.42, $p < 0.0001$; (adjusted) regression beta (SE) 1.2 (0.092), $p < 0.001$.

Self-rated activity relative to others ones age also related strongly to multiple measures known to predict health, healthcare utilization and mortality, such as general self-rated health, energy, tiredness, depression (CES-D), sleep, muscular weakness, fatigue with exertion, and metabolic syndrome factors of HDL, triglycerides, BMI, waist circumference and serum glucose (**Table 1**).

Self-rated relative physical activity showed a graded positive relation to age on unadjusted analysis (p<0.001) (**Table 2**). This was true in each the clinical trial sample and the observational study sample. Findings were monotonic in the observational sample, and nearly so in the clinical trial sample for subjects from their 40s to 80s.

Multivariable regression (**Table 3**) affirmed that a significant relation of age to reported relative activity was retained with adjustment for variables (sex, ethnicity and education level) that could relate to both age and activity of participants (p<0.001).

Discussion

To our knowledge this is the first explicit demonstration that progressively older study subjects may depart successively more from parity with those they are taken to represent. This was found in exemplars of both observational studies and clinical trials. Adults in their 30s and 40s reported being only modestly more active than others their age (closest to "about as active" as others). By the oldest decades, participants had surpassed the "somewhat more active" mark, even on average, and were partway, on average, toward the maximum rating of "much more active" compared to others their age. These differences by age were strongly significant.

This finding is concordant with expectations that might be generated from previous observations linking study participation with higher health and vitality. All subjects who self-select for study participation may differ in systematic ways from the target population or population as a whole[8-11]. Prior studies have noted that clinical trial participants are generally younger and healthier than referred and registry patients[4]. Our results further show that successively older subjects *who do* participate in research studies may be successively less typical of their age cohort in a metric with an expected – and indirectly observed – relation to health. For instance, it related to general self-rated health, which has been found to strongly predict physical function/disability, health care utilization, and mortality[14-16]. Relative activity also related in expected directions to other assessed factors known to predict health and mortality in elderly, such as fasting glucose[18], white blood cell count[19], HDL-cholesterol[20], sleep problems[21 22], and depression[23-29].

Selective participation by healthier elderly has potential to influence trial outcomes. This is particularly true for outcomes for which vitality, function, activity, or any of the range of health-relevant correlates of relative activity, may serve as effect modifiers. (Such health correlates include those elucidated here, and presumably many others that were not examined.) The study also has relevance for outcomes for which differences in subjects' activity and/or function, through their relation to expected health, may modify study power. For example, a doubling or halving of mortality by an intervention (or with a risk factor), even in the absence of effect modification, will have lower statistical power in a sample with lower baseline risk of mortality outcomes (as a healthier sample portends). Healthier elderly may reduce power for the risk-side of the equation, which can shift the apparent risk-benefit balance.

Limitations of the present analysis are several. Activity relative to others of the same age was assessed by self-report. Objective evaluation of nonparticipants, to permit direct comparison, is inherently problematic (as they have not consented to participate). This limitation is mitigated by demonstration of strongly significant relationships of relative activity to health predictors within the study population. (A relation to hard outcomes could not be assessed: the observational study was not longitudinal, and the trial sample enrolled generally healthy participants with only six-months follow-up.)

It is possible that subjects may over-represent their functional state relative to others; but this would not produce an expected age association. In principle, older subjects may differ from younger subjects in the manner of such amplification, but there is little reason to believe this is the case, and the age-adjusted association of our relative activity measure to an exercise frequency measure further diminishes this concern. There is reason to predict that as limiting comorbidities and disabilities accrue with rising age, and as function and the ability to sustain activity declines progressively with age, more elderly individuals will more often find participation too burdensome – yielding a successively more rarefied sample that is progressively more nonrepresentatively robust and healthy, compatible with the findings shown. Indeed, better health has been reported to influence self-selection for participation in studies in general[1], an observation that might be predicted to drive the finding observed, since health problems increase in prevalence with increasing age.

Factors driving self-selection for participation may vary depending on the character of the study. Although theoretical considerations suggest our findings may generalize broadly, other studies should evaluate how these findings are moderated based on the type of study and condition being examined.

In conclusion, as subject age advances, those who participate in clinical trials and observational studies may depart increasingly from those they are taken to represent, in physical activity and, likely, in health. This potential lack of representativeness should be borne in mind when interpreting studies that include, or focus upon, older subjects. Our finding has fundamental implications for how results in elderly study participants may reflect on elderly more generally, implications which rise in importance as the population continues to age.

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Disclaimers

Competing Interest Statement: *All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that all authors have no relationships with any companies that might have an interest in the submitted work in the previous 3 years; nor do their spouses, partners, or children have any financial relationships that may be relevant to the submitted work; and none of the authors have any non-financial interests that may be relevant to the submitted work.*

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Author Contributions: All authors, external and internal, had full access to all of the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis.

The authors certify that this manuscript represents valid work and has not been published or is currently under consideration for publication elsewhere.

Data Sharing: Technical appendix, statistical code, and dataset available from the corresponding author (bgolomb@ucsd.edu).

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Table 1. Activity Ratings by Age

	Clinical Trial Sample		Observational Sample	
Age Decade	N	Relative Activity* Mean (SD)	N	Relative Activity* Mean (SD)
30s	80	3.35 (1.02)	34	3.26 (1.24)
40s	180	3.30 (1.20)	565	3.27 (1.23)
50s	308	3.49 (1.20)	650	3.68 (1.15)
60s	261	3.92 (1.07)	569	3.94 (1.05)
70s	151	3.89 (1.01)	512	3.97 (1.04)
80s	20	4.10 (1.07)	24	4.17 (1.31)
Significance of Change by Age Decade		P < 0.001		P < 0.001

N – Number; SD – Standard deviation
* Level of physical activity "compared to other persons your age" measured on a 5-point Likert scale: 1=much less active, 2=somewhat less active, 3=about as active, 4=somewhat more active, 5=much more active.

Table 2. Older Participant Age Associated with Greater Self-reported Relative Activity Level, Ordinal Logit Analyses

	Clinical Trial Sample				Observational Sample			
	Coefficient for Age Decade	Standard Error	p-value	95% Confidence Interval	Coefficient for Age Decade	Standard Error	p-value	95% Confidence Interval
Unadjusted	0.29	0.044	<0.001	0.21, 0.38	0.37	0.034	<0.001	0.31, 0.44
Multivariable adjusted*	0.35	0.052	<0.001	0.25, 0.45	0.37	0.035	<0.001	0.30, 0.44

- Ordinal logit, Activity level as outcome, adjusted for age, gender, ethnicity, and education level.

Table 3: Self-Rated Relative Activity*: Predicts Health-Predictors in Age > 50*

Variable	Correlation Coefficient	P-value	Regression Coefficient age adjusted*	P-value	*Age Relation*
Times/wk exercise at least 20minutes	0.42	**<0.0001**	1.2 (0.092)	**<0.001**	*(-) 0.024*
CES-D (0-52)	-0.21	**<0.0001**	-1.3 (0.23)	**<0.001**	*NS*
Depressed (0-10)	-0.13	**0.0083**	-0.21 (0.086)	**0.017**	*NS*
Energy (0-10)	0.21	**<0.0001**	0.34 (0.064)	**<0.001**	*(+) 0.031*
Sleep problems (0-10)	-0.084	**0.028**	-0.21 (.095)	**0.024**	*NS*
Sleep quality (0-30)	0.078	**0.036**	0.037 (0.011)	**0.001**	*(+) 0.081*
Tired (0-10)	-0.29	**<0.0001**	-0.72 (0.13)	**<0.001**	*(+) 0.001*
Muscle weakness	-0.14	**<0.0001**	-0.29 (0.070)	**<0.001**	*(+) 0.005*
Fatigue w Exertion (0-10)	-0.26	**<0.0001**	-0.61 (0.12)	**<0.001**	*(+) 0.002*
Health (0-10)	0.20	**<0.0001**	0.31 (0.061)	**<0.001**	*(+) 0.071*
Satisfaction with health (0-100)	0.30	**<0.0001**	5.6 (0.69)	**<0.001**	*NS*
Glucose (mg/dL)*	-0.073	**0.049**	-0.73 (0.31)	**0.019**	*(+) 0.014*
HDL (mg/dL)	0.10	**0.0063**	1.2 (0.53)	**0.028**	*(+) 0.001*
Triglycerides (mg/dL)	-0.17	**<0.0001**	-10 (2.3)	**<0.001**	*NS*
Body mass index	-0.26	**<0.0001**	-0.97 (0.15)	**<0.001**	*(-) 0.002*
Waist (cm)	-0.23	**<0.0001**	-3.9 (0.63)	**<0.001**	*NS*
Platelets	-0.073	**0.051**	-2.7 (1.7)	**0.11**	*(-) 0.043*
White blood cell count	-0.08	**0.027**	-0.125 (0.050)	**+0.012**	*(+) 0.058*

*Relative Activity level for age as the predictor, with age as an adjusted covariate in the regressions, in age > 50
†Note: patients with diabetes or measured glucose over 142 were excluded. This finding is thus despite range restriction.
Note that in these study *participants*, there is a "paradoxically" favorable age association for some variables that generally worsen with rising age, including energy, sleep quality, health, and HDL-cholesterol.

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Abstract

Objective: Study participants can differ from the target population they are taken to represent. We sought to investigate whether older age magnifies such differences, examining age-trends, among study participants, in self-rated level of activity compared to others of the same age.

Design: Cross-sectional examination of the relation of participant age to reported "relative activity" (i.e. compared to others of the same age), a bidirectionally-correlated proxy for relative vitality, in exemplars of randomized and observational studies.

Setting: University of California, San Diego (UCSD)

Participants: 2,404 adults age 40-79 including employees of UCSD, and their partners (San Diego Population Study, observational study). 1,016 adults not on lipid medications and without known heart disease, diabetes, cancer or HIV (UCSD Statin Study, randomized trial).

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Results: Successively older participants reported successively greater activity relative to others their age (greater departure from the norm for their age), p<0.001 in both studies. Relative activity significantly predicted (in regression adjusted for age) actual activity (times/week exercised); and numerous self-rated and objective health-predictors. These included general self-rated health, CES-D (depression score), sleep, tiredness, energy; body mass index, waist circumference, serum glucose, HDL-cholesterol, triglycerides, and white blood cell count. Indeed some health-predictor associations with age in participants were "paradoxical," consistent with greater apparent health in older age – for study participants.

Conclusion: Study participants may not be representative of the population they are intended to reflect. Our results suggest that departures from representativeness may be amplified with increasing subject age.

Trial Registration: UCSD Statin Study – Clinicaltrials.gov # NCT00330980 (http://ClinicalTrials.gov)

Keywords: elderly; representativeness; sample selection; generalizability; clinical trials, subject characteristics

Abbreviations: UCSD – University of California, San Diego

Introduction

Relevance of data from human research studies to the general population depends on the similarity of study participants to those they are taken to represent, i.e. the “target” population. It is recognized that study samples may differ from the target population[1 2]. Often the study sample directly or disproportionately excludes the elderly[3-5] who have worse health and higher expected mortality[6], and who may differ from younger participants in treatment effects.

Although there has been increasing emphasis (at least in principle) on inclusion of the elderly in studies[7], there are reasons for concern that elderly study participants may be less representative of their age group than younger participants.

Self-selection by participants themselves of a relatively healthier and more functional study population may occur in all ages[8-11], since even morbidity not requiring exclusion may nonetheless inhibit participation[1]. But since health problems and functional limitations that lead to self-exclusion may increasingly affect those older in age, we theorized that older age participants might be progressively less representative in indices relevant to function and vitality. Direct comparison of consenting participants to nonparticipants is problematic, since inherently the researcher has access only to the former group. Participants’ ratings of themselves relative to others their age provides a tentative approach to evaluate whether departures rise with age, if such relative measures can be validated against direct measures.

We validated “relative-activity,” that is, self-rated activity-level *compared to other individuals of the same age*, against an activity metric that is absolute (vs relative); and assessed its relation to health-relevant outcomes. We examined reported relative-activity, compared to other individuals ones age, from available exemplars of two types of medical studies (observational and randomized controlled trial) to evaluate whether reported departure from normative function rises with increasing participant age.

Methods

Randomized Controlled Trial Participants:

1,016 male and female participants age 20-85 from the San Diego area were enrolled in the UCSD Statin Study, a double-blind, randomized, placebo-controlled trial assessing effects of statin cholesterol-lowering drugs on a relatively broadly sampled group of adults (a primary prevention sample). There was no imposed upper age limit. Participants were men over age 20 and surgically or chronologically postmenopausal women not on lipid medications and without extremes of LDL-cholesterol (high or low), diagnosed cardiovascular disease, diabetes or HIV. More information on study population and design is available elsewhere[12].

Observational Study Participants:

2,404 selected men and women ages 40-79 were enrolled in the San Diego Population Study, a population-based observational study identifying prevalence of arterial and venous disease. Participants were drawn from current and former employees of the University of California San Diego (**UCSD**), as well as their spouses/ significant others – inclusion of which modestly extended the age range of participants in both directions[13]. In addition, a small number of non-UCSD volunteers were included. Participants represented a spectrum of socioeconomic status, including unemployed and retired as well as working persons. A full description of the study population is available elsewhere[13].

Both studies were approved by the UCSD Human Research Protections Program, and all participants gave informed consent to participate.

Relative Activity variable:

Participants in both studies were asked to rate their level of physical activity "Compared to other persons your age" on a 5-point Likert scale (1=much less active, 2=somewhat less active, 3=about as active, 4=somewhat more active, 5=much more active). We refer to this activity rating as "relative activity." Single-item self-rated assessments have shown strong predictive validity[14-16].

Validation Variables:

Other measures used: From the randomized trial, several other variables were chosen against which to validate the relative activity variable. All variables were assessed at baseline (prior to study treatment).

Absolute activity: We validated the relation of this relative activity measure to self-reported actual exercise frequency (number of episodes of vigorous exercise for at least 20 minutes over a week). Direct measurements of activity was not performed, but self-reported exercise-frequency related significantly to objective measures known to be affected by exercise (e.g. body mass index, triglycerides, HDL-cholesterol, each p<0.001) in age-sex adjusted analysis.

Health Predictor Variables: Self-rated and questionnaire variables known to predict mortality and health outcomes that were considered against *relative* activity included depressed mood (Center for Epidemiological Studies – Depression Scale aka CES-D, and self-rated), and single-item self-ratings of energy, tiredness, muscle weakness, fatigue with exertion, overall health, and satisfaction with health. Objective measures included platelet count (acute phase reactant), white blood count, serum glucose, HDL-cholesterol, triglycerides, body mass index (BMI), and waist circumference.

Analyses:

Self-rated relative activity was tabulated by age decade. For each study, significance of self-rated relative activity change with age assessed across the full age range. Activity associations and health implications of the relative activity measure were examined in older study participants (age > 50) from the randomized trial sample (in which these health variables were assessed), using correlation; and also regression analysis. (Both by expectation and empirically in this sample, people in their 30s and 40s were comparatively similar in their self-rated relative activity, consistent with the expectation that age-related health conditions are not yet strongly present, leading to the emphasis on those over age 50.) In the latter, age-relative activity was the independent variable, and assessments were adjusted for actual age.

For both study samples, we conducted bivariate analyses examining reported relative activity level as a function of age decade. This was followed by multivariable regression using ordinal logit with robust standard errors (aka White standard errors)[17] controlling for sex, ethnicity (categorical variable) and education (scaled from 1=grade school or less to 9=doctoral degree).

All analyses were conducted using Stata™ version 8.0; StataCorp, College Station, Texas. Two-sided P-values less than 0.05 were designated statistically significant.

Results

Self-reported activity relative to others ones age related strongly to actual activity: (unadjusted) correlation 0.42, $p < 0.0001$; (adjusted) regression beta (SE) 1.2 (0.092), $p < 0.001$.

Self-rated activity relative to others ones age also related strongly to multiple measures known to predict health, healthcare utilization and mortality, such as general self-rated health, energy, tiredness, depression (CES-D), sleep, muscular weakness, fatigue with exertion, and metabolic syndrome factors of HDL, triglycerides, BMI, waist circumference and serum glucose (**Table 1**).

Self-rated relative physical activity showed a graded positive relation to age on unadjusted analysis ($p<0.001$) (**Table 2**). This was true in both the clinical trial sample and the observational study sample. Findings were monotonic in the observational sample, and nearly so in the clinical trial sample for participants from their 40s to 80s.

Multivariable regression (**Table 3**) affirmed that a significant relation of age to reported relative activity was retained with adjustment for variables (sex, ethnicity and education level) that could relate to both age and activity of participants ($p<0.001$).

Discussion

To our knowledge this is the first explicit demonstration that progressively older study participants may depart successively more from parity with those they are taken to represent, in observational and clinical trial settings. This was found in exemplars of both observational studies and clinical trials. Adults in their 30s and 40s reported being only modestly more active than others their age (closest to “about as active” as others). By the oldest decades, participants had surpassed the “somewhat more active” mark, even on average, and were partway, on average, toward the maximum rating of "much more active" compared to others their age. These differences by age were strongly significant.

This finding is concordant with expectations that might be generated from previous observations linking study participation with higher health and vitality. All participants who self-select for study participation may differ in systematic ways from the target population or population as a whole[8-11]. Prior studies have noted that clinical trial participants are generally younger and healthier than referred and registry patients[4]. Our results further show that successively older participants *who do* participate in research studies may be successively less typical of their age cohort in a metric with an expected – and indirectly observed – relation to health. For instance, it related to general self-rated health, which has been found to strongly predict physical function/disability, health care utilization, and mortality[14-16]. Relative activity also related in expected directions to other assessed factors known to predict health and mortality in elderly, such as fasting glucose[18], white blood cell count[19-21], HDL-cholesterol[22], sleep problems[23 24], and depression[25-31].

Our evidence accords with and extends recent evidence from survey studies. Participants who indicated (on a survey) they would volunteer for an exercise study reported less physical function decline, more physical activity and less chronic pain than those who would not, as well as worse self-reported health[32]; however, these reflect hypothetical intentions rather than participation, and the fashion in which participants were shown to be differential focused largely on domains that may affect comfort and performance for that study's assessments. A survey study of Finns aged 52-76 found that "Favorable health was generally more frequent among respondents than nonrespondents," gauging health status by medicine reimbursements (ascertained by linking to register data)[33]. Whether disparities progressed successively as age advanced was not ascertained.

Selective participation by healthier elderly has potential to influence trial outcomes. This is particularly true for outcomes for which vitality, function, activity, or any of the range of health-relevant correlates of relative activity, may serve as effect modifiers. (Such health correlates include those elucidated here, and presumably many others that were not examined.) The study also has relevance for outcomes for which differences in participants' activity and/or function, through their relation to expected health, may modify study power. For example, a doubling or halving of mortality by an intervention (or with a risk factor), even in the absence of effect modification, will have lower statistical power in a sample with lower baseline risk of mortality outcomes (as a healthier sample portends). Healthier elderly may reduce power for the risk-side of the equation, which can shift the apparent risk-benefit balance.

Limitations of the present analysis are several. Activity relative to others of the same age was assessed by self-report. Objective evaluation of nonparticipants, to permit direct comparison, is inherently problematic (as they have not consented to participate). This limitation is mitigated by demonstration of strongly significant relationships of relative activity to health predictors within the study population. (A relation to hard outcomes like mortality could not be assessed: the observational study was not longitudinal, and the trial sample enrolled generally healthy participants with only six-months follow-up.)

It is possible that participants may over-represent their functional state relative to others; but this would not produce an expected age association. In principle, older participants may differ from younger participants in the manner of such amplification, but there is little reason to believe this is the case, and the age-adjusted association of our relative activity measure to an exercise frequency measure further diminishes this concern. There is reason to predict that as limiting comorbidities and disabilities accrue with rising age, and as function and the ability to sustain activity declines progressively with age, more elderly individuals will more often find participation too burdensome – yielding a successively more rarefied sample that is progressively more nonrepresentatively robust and healthy, compatible with the findings shown. Indeed, better health has been reported to influence self-selection for participation in studies in general[1], an observation that might be predicted to drive the finding observed, since health problems increase in prevalence with increasing age.

Factors driving self-selection for participation may vary depending on the character of the study. Although theoretical considerations suggest our findings may generalize broadly, other studies should evaluate how these findings are moderated based on the type of study and condition being examined.

One unsettling implication is that clinical guidelines lack a meaningful evidence basis, when applied to those of older age. Concerns have previously been expressed that when "evidence based" study findings *based on younger individuals* are implemented in elderly patients with comorbidities, via clinical practice guidelines reinforced by performance pay, this may result in perverse incentives that may diminish rather than enhance quality of care for elderly[34], by promoting promiscuous polypharmacy. Our findings suggest such concerns obtain even when recommendations derive from data actually procured in elderly participants. (Analogous concerns may apply, irrespective of age, for patients with multiple comorbidities, polypharmacy, dementia, disability, limited life expectancy, and/or past adverse responses to the recommended treatment – groups that, like elderly, often bear less favorable risk-benefit prospects.)

For older elderly, some have urged a more individualized "less is more" approach placing greater emphasis on clinical judgment, quality of life, and in-depth consultation with the patient and family[34-36]. This seems rational, given 1) absence of applicable evidence that medication benefits similarly apply, 2) increased medication burden, as age-related morbidities accrue, 3) amplified risk of drug adverse events, drug interactions and medication-taking errors in elderly with implications to quality of life and function, 4) magnified impact of added functional compromise in the elderly; coupled with 5) evidence, albeit non-randomized, suggesting striking subjective and objective benefits among elderly when systematic discontinuation of medications is undertaken[35 36].

In conclusion, as age advances, those who participate in clinical trials and observational studies may depart increasingly from those they are taken to represent. That is, real patients may depart increasingly from (an ever more rarefied, nonrepresentative, healthiest subsegment of) the elderly population that volunteers to participate in clinical studies, rendering study findings of increasingly doubtful applicability. This magnifies concerns that, as the elderly swell as a fraction of the population the chasm may grow, between what is recommended based on "evidence," and what is best for the patient.

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Disclaimers

Competing Interest Statement: *All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that all authors have no relationships with any companies that might have an interest in the submitted work in the previous 3 years; nor do their spouses, partners, or children have any financial relationships that may be relevant to the submitted work; and none of the authors have any non-financial interests that may be relevant to the submitted work.*

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Author Contributions: Golomb was PI on the randomized trial, provided the concept, and generated the initial draft. Chan worked with Golomb to perform initial analyses and early revisions to the manuscript. Criqui was PI on the observational study, co-PI on the randomized trial, and provided access to the observational data. White provided senior statistical oversight and conceptual and editorial input. Evans conducted literature reviews on risk factors and worked with Golomb on an intermediate set of revisions. Koperski created Stata do-files, replicated the findings, reviewed all findings for correctness with Golomb, and performed editorial and administrative aspects of submission. All authors reviewed the manuscript for intellectual content.

Data Sharing: Technical appendix, statistical code, and dataset available from the corresponding author (bgolomb@ucsd.edu).

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Table 1. Self-Rated "Relative Activity"* Relates to Health-Predictors (Age >50)

Variable	Correlation Coefficient	P-value	Regression Coefficient, age adjusted†	P-value	*Age Relation, sign and P-value*
Times/wk exercise at least 20minutes	0.42	**<0.0001**	1.2 (0.092)	**<0.001**	*(-) 0.024*
CES-D (0-52)	-0.21	**<0.0001**	-1.3 (0.23)	**<0.001**	*NS*
Depressed (0-10)	-0.13	**0.0083**	-0.21 (0.086)	**0.017**	*NS*
Energy (0-10)	0.21	**<0.0001**	0.34 (0.064)	**<0.001**	*(+) 0.031*
Sleep problems (0-10)	-0.084	**0.028**	-0.21 (.095)	**0.024**	*NS*
Sleep quality (0-30)	0.078	**0.036**	0.037 (0.011)	**0.001**	*(+) 0.081*
Tired (0-10)	-0.29	**<0.0001**	-0.72 (0.13)	**<0.001**	*(+) 0.001*
Muscle weakness	-0.14	**<0.0001**	-0.29 (0.070)	**<0.001**	*(+) 0.005*
Fatigue w Exertion (0-10)	-0.26	**<0.0001**	-0.61 (0.12)	**<0.001**	*(+) 0.002*
Health (0-10)	0.20	**<0.0001**	0.31 (0.061)	**<0.001**	*(+) 0.071*
Satisfaction with health (0-100)	0.30	**<0.0001**	5.6 (0.69)	**<0.001**	*NS*
Glucose (mg/dL) ‡	-0.073	**0.049**	-0.73 (0.31)	**0.019**	*(+) 0.014*
HDL (mg/dL)	0.10	**0.0063**	1.2 (0.53)	**0.028**	*(+) 0.001*
Triglycerides (mg/dL)	-0.17	**<0.0001**	-10 (2.3)	**<0.001**	*NS*
Body mass index	-0.26	**<0.0001**	-0.97 (0.15)	**<0.001**	*(-) 0.002*
Waist (cm)	-0.23	**<0.0001**	-3.9 (0.63)	**<0.001**	*NS*
Platelets	-0.073	**0.051**	-2.7 (1.7)	**0.11**	*(-) 0.043*
White blood cell count	-0.08	**0.027**	-0.125 (0.050)	**+0.012**	*(+) 0.058*

CES-D – Center for Epidemiological Studies -Depression scale, HDL – high density lipoprotein cholesterol, NS – non-significant.
* Level of activity "compared to other persons your age" measured on a 5-point Likert scale: 1=much less active, 2=somewhat less active, 3=about as active, 4=somewhat more active, 5=much more active.
† Regression examines relative activity level relation to health predictor, among those age > 50, with age as an adjusted covariate in the regressions.
(The column to the far right gives the sign of the coefficient for the age variable, and its significance.)
‡ Note: patients with diabetes or measured glucose over 142 were excluded. This finding is thus despite range restriction.
Note that in these study participants, there is a "paradoxically" favorable age association for some variables that generally worsen with rising age, including energy, sleep quality, health, and HDL-cholesterol.

Table 2. "Relative-Activity" Ratings*, by Age

	Clinical Trial Sample		Observational Sample	
Age Decade	N	Relative Activity* Mean (SD)	N	Relative Activity* Mean (SD)
30s	80	3.35 (1.02)	34	3.26 (1.24)
40s	180	3.30 (1.20)	565	3.27 (1.23)
50s	308	3.49 (1.20)	650	3.68 (1.15)
60s	261	3.92 (1.07)	569	3.94 (1.05)
70s	151	3.89 (1.01)	512	3.97 (1.04)
80s	20	4.10 (1.07)	24	4.17 (1.31)
Significance of Change by Age Decade		P < 0.001		P < 0.001

N – Number; SD – Standard deviation
* Level of physical activity "compared to other persons your age" measured on a 5-point Likert scale: 1=much less active, 2=somewhat less active, 3=about as active, 4=somewhat more active, 5=much more active.

Table 3. Older Participant Age Associated with Greater Self-reported "Relative-Activity"*, Ordinal Logit Analyses

	Clinical Trial Sample				**Observational Sample**			
	Coefficient for Age Decade	Standard Error	P-value	95% CI	Coefficient for Age Decade	Standard Error	P-value	95% CI
Unadjusted	0.29	0.044	<0.001	0.21, 0.38	0.37	0.034	<0.001	0.31, 0.44
Multivariable adjusted†	0.35	0.052	<0.001	0.25, 0.45	0.37	0.035	<0.001	0.30, 0.44

CI – Confidence interval

* Level of activity "compared to other persons your age" measured on a 5-point Likert scale: 1=much less active, 2=somewhat less active, 3=about as active, 4=somewhat more active, 5=much more active.

†Ordinal logit adjusted for age, gender, ethnicity, and education level.

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The Older the Better:

Are Elderly Study Participants More Nonrepresentative?

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Abstract

Objective: Study ~~subjects~~participants can differ from the target population they are taken to represent. ~~We sought to investigate whether age modifies such differences~~We sought to investigate whether older age magnifies such differences, examining age-trends, among study participants, in self-rated level of activity compared to others of the same age.~~ in terms of relative activity~~~~investigate whether age modifies such differences.~~

Design: Cross-sectional examination of the relation of participant age to reported "relative activity" (i.e. compared to others of the same age), a bidirectionally-correlated proxy for relative vitality, in exemplars of randomized and observational studies.

Setting: University of California, San Diego (UCSD)

Participants: 2,404 adults age 40-79 including employees of UCSD, and their partners (San Diego Population Study, observational study). 1,016 adults not on lipid medications and without known heart disease, diabetes, cancer or HIV (UCSD Statin Study, randomized trial).

Measurements: Self-rated activity relative to others one's age, 5-point Likert Scale, was evaluated by age decade; and related via correlation and regression to a suite of health-relevant subjective and objective outcomes.

Results: Successively older participants reported successively greater activity relative to others their age (greater departure from the norm for their age), p<0.001 in both studies. Relative activity significantly predicted (in regression adjusted for age) actual activity (times/week exercised); and numerous self-rated and objective health-predictors. These included general self-rated health, CES-D (depression score), sleep, tiredness, energy; body mass index, waist circumference, serum glucose, HDL-cholesterol, triglycerides, and white blood cell count.

Indeed some health-predictor associations with age in participants were "paradoxical," consistent with greater apparent health in older age – for study participants.

Conclusion: Study participants may not be representative of the population they are intended to reflect. Our results suggest that departures from representativeness may be amplified with increasing subject age.

Trial Registration: UCSD Statin Study – Clinicaltrials.gov # NCT00330980 (http://ClinicalTrials.gov)

Keywords: elderly; representativeness; sample selection; generalizability; clinical trials, subject characteristics

Abbreviations: UCSD – University of California, San Diego

~~**What this paper adds:**~~

~~Section 1 – What is already known about the subject?~~

~~Study participants differ from the general population they are taken to represent and may be healthier.~~

~~Section 2 – What this study adds~~

~~This study demonstrated that with increasing age, self-selected study participants diverge increasingly from the population they are taken to represent. This has implications for studies of, and including, elderly subjects; affecting generalizability to older real-world populations.~~

Introduction

Relevance of data from human research studies to the general population depends on the similarity of study participants to those they are taken to represent, i.e. the "target" population. It is recognized that study samples may differ from the target population[1 2]. Often the study sample directly or disproportionately excludes the elderly[3-5] who have worse health and higher expected mortality[6], and who may differ from younger ~~subjects~~participants in treatment effects.

Although there has been increasing emphasis (at least in principle) on inclusion of the elderly in studies[7], there are reasons for concern that elderly study participants may be less representative of their age group than younger ~~subjects~~participants.

Self-selection by ~~subjects~~participants themselves of a relatively healthier and more functional study population may occur in all ages[8-11], since even morbidity not requiring exclusion may nonetheless inhibit participation[1]. But since health problems and functional limitations that lead to self-exclusion may increasingly affect those older in age, we theorized that older age participants might be progressively less representative in indices relevant to function and vitality. Direct comparison of consenting participants to nonparticipants is problematic, since inherently the researcher has access only to the former group. ~~Subjects~~Participants' ratings of themselves relative to others their age provides a tentative approach to evaluate whether departures rise with age, if such relative measures can be validated against direct measures.

We validated "relative-activity," that is, self-rated activity-level *compared to other individuals* ~~*ones age*~~*of the same age*, against an activity metric that is absolute (vs relative); and assessed its relation to health-relevant outcomes. We examined reported relative-activity, compared to other individuals ones age, from available exemplars of two types of medical studies (observational and randomized controlled trial) to evaluate whether reported departure from normative function rises with increasing participant age.

Methods

Randomized Controlled Trial ~~Subjects~~Participants:

1,016 male and female ~~subjects~~participants age 20-85 from the San Diego area were enrolled in the UCSD Statin Study, a double-blind, randomized, placebo-controlled trial assessing effects of statin cholesterol-lowering drugs on a relatively broadly sampled group of adults (a primary prevention sample). There was no imposed upper age limit. ~~Subjects~~Participants were men over age 20 and ~~nonprocreative~~ surgically or chronologically postmenopausal women not on lipid medications and without extremes of LDL-cholesterol (high or low), diagnosed cardiovascular disease, diabetes or HIV. More information on study population and design is available elsewhere[12].

Observational Study ~~Subjects~~Participants:

2,404 selected men and women ages 40-79 were enrolled in the San Diego Population Study, a population-based observational study identifying prevalence of arterial and venous disease. ~~Subjects~~Participants were drawn from current and former employees of the University of California San Diego (**UCSD**), as well as their spouses/ significant others – inclusion of which modestly extended the age range of participants in both directions[13]. In addition, a small number of non-UCSD volunteers were included. ~~Subjects~~Participants represented a spectrum of socioeconomic status, including unemployed and retired as well as working persons. A full description of the study population is available elsewhere[13].

Both studies were approved by the UCSD Human Research Protections Program, and all ~~subjects~~participants gave informed consent to participate.

Relative Activity variable:

Participants in both studies were asked to rate their level of physical activity “Compared to other persons your age”~~In both studies, “activity relative~~ compared “~~to others your age” was queried at baseline and measured~~ on a 5-point Likert scale (1=much less active, 2=somewhat less active, 3=about as active, 4=somewhat more active, 5=much more active). We refer to this activity rating as “relative activity.” Single-item self-rated assessments have shown strong predictive validity[14-16].

Validation Variables:

Other measures used: From the randomized trial, several other variables were chosen against which to validate the relative activity variable. All variables were assessed at baseline (prior to study treatment).

Absolute activity: We validated the relation of this relative activity measure to self-reported actual exercise frequency (number of episodes of vigorous exercise for at least 20 minutes over a week). Direct measurements of activity was not performed, but self-reported exercise-frequency related significantly to objective measures known to be affected by exercise (e.g. body mass index, triglycerides, HDL-cholesterol, each $p<0.001$) in age-sex adjusted analysis~~)~~..

Health Predictor Variables: Self-rated and questionnaire variables known to predict mortality and health outcomes that were considered against *relative* activity included depressed mood

(Center for Epidemiological Studies – Depression Scale aka CES-D, and self-rated), and single-item self-ratings of energy, tiredness, muscle weakness, fatigue with exertion, overall health, and satisfaction with health. Objective measures included platelet count (acute phase reactant), white blood count, serum glucose, HDL-cholesterol, triglycerides, body mass index (BMI), and waist circumference.

Analyses:

Self-rated relative activity was tabulated by age decade. For each study, significance of self-rated relative activity change with age assessed across the full age range. Activity associations and health implications of the relative activity measure were examined in older study participants (age > 50)~~)~~ from the randomized trial sample (in which these health variables were assessed), using correlation; and also regression analysis. (Both by expectation and empirically in this sample, people in their 30s and 40s were comparatively similar in their self-rated relative activity, consistent with the expectation that age-related health conditions are not yet strongly present, leading to the emphasis on those over age 50.) In the latter, age-relative activity was the independent variable, and assessments were adjusted for actual age.

For both study samples, we conducted bivariate analyses examining reported relative activity level as a function of age decade. This was followed by multivariable regression using ordinal logit with robust standard errors (aka White standard errors)[17] controlling for sex, ethnicity (categorical variable) and education (scaled from 1=grade school or less to 9=doctoral degree).

All analyses were conducted using Stata™ version 8.0; StataCorp, College Station, Texas. Two-sided P-values less than 0.05 were designated statistically significant.

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Results

Self-reported activity relative to others ones age related strongly to actual activity: (unadjusted) correlation 0.42, $p < 0.0001$; (adjusted) regression beta (SE) 1.2 (0.092), $p < 0.001$.

Self-rated activity relative to others ones age also related strongly to multiple measures known to predict health, healthcare utilization and mortality, such as general self-rated health, energy, tiredness, depression (CES-D), sleep, muscular weakness, fatigue with exertion, and metabolic syndrome factors of HDL, triglycerides, BMI, waist circumference and serum glucose (**Table 1**).

Self-rated relative physical activity showed a graded positive relation to age on unadjusted analysis (p<0.001) (**Table 2**). This was true in ~~each~~ both the clinical trial sample and the observational study sample. Findings were monotonic in the observational sample, and nearly so in the clinical trial sample for ~~subjects~~participants from their 40s to 80s.

Multivariable regression (**Table 3**) affirmed that a significant relation of age to reported relative activity was retained with adjustment for variables (sex, ethnicity and education level) that could relate to both age and activity of participants (p<0.001).

Discussion

To our knowledge this is the first explicit demonstration that progressively older study ~~subjects~~participants may depart successively more from parity with those they are taken to represent, in observational and clinical trial settings. This was found in exemplars of both observational studies and clinical trials. Adults in their 30s and 40s reported being only modestly more active than others their age (closest to "about as active" as others). By the oldest decades, participants had surpassed the "somewhat more active" mark, even on average, and were partway, on average, toward the maximum rating of "much more active" compared to others their age. These differences by age were strongly significant.

This finding is concordant with expectations that might be generated from previous observations linking study participation with higher health and vitality. All ~~subjects~~participants who self-select for study participation may differ in systematic ways from the target population or population as a whole[8-11]. Prior studies have noted that clinical trial participants are generally younger and healthier than referred and registry patients[4]. Our results further show that successively older ~~subjects~~participants *who do* participate in research studies may be successively less typical of their age cohort in a metric with an expected – and indirectly observed – relation to health. For instance, it related to general self-rated health, which has been found to strongly predict physical function/disability, health care utilization, and mortality[14-16]. Relative activity also related in expected directions to other assessed factors known to predict health and mortality in elderly, such as fasting glucose[18], white blood cell count[19-21], HDL-cholesterol[22], sleep problems[23 24], and depression[25-31].

Our evidence accords with and extends recent evidence from survey studies. ~~Subjects~~Participants who indicated (on a survey) they would volunteer for an exercise study reported less physical function decline, more physical activity and less chronic pain than those who would not, as well as worse self-reported health[32]; however, these reflect hypothetical intentions rather than participation, and the fashion in which ~~subjects~~participants were shown to be differential focused largely on domains that may affect comfort and performance for that study's assessments. A survey study of Finns aged 52-76 found that "Favorable health was generally more frequent among respondents than nonrespondents," gauging health status by medicine reimbursements (ascertained by linking to register data)[33]. Whether disparities progressed successively as age advanced was not ascertained.

Selective participation by healthier elderly has potential to influence trial outcomes. This is particularly true for outcomes for which vitality, function, activity, or any of the range of health-relevant correlates of relative activity, may serve as effect modifiers. (Such health correlates include those elucidated here, and presumably many others that were not examined.) The study also has relevance for outcomes for which differences in ~~subjects~~participants' activity and/or function, through their relation to expected health, may modify study power. For example, a doubling or halving of mortality by an intervention (or with a risk factor), even in the absence of effect modification, will have lower statistical power in a sample with lower baseline risk of mortality outcomes (as a healthier sample portends). Healthier elderly may reduce power for the risk-side of the equation, which can shift the apparent risk-benefit balance.

Limitations of the present analysis are several. Activity relative to others of the same age was assessed by self-report. Objective evaluation of nonparticipants, to permit direct comparison, is inherently problematic (as they have not consented to participate). This limitation is mitigated by demonstration of strongly significant relationships of relative activity to health predictors within the study population. (A relation to hard outcomes like mortality could not be assessed: the observational study was not longitudinal, and the trial sample enrolled generally healthy participants with only six-months follow-up.)

It is possible that ~~subjects~~participants may over-represent their functional state relative to others; but this would not produce an expected age association. In principle, older

~~subjects~~participants may differ from younger ~~subjects~~participants in the manner of such amplification, but there is little reason to believe this is the case, and the age-adjusted association of our relative activity measure to an exercise frequency measure further diminishes this concern. There is reason to predict that as limiting comorbidities and disabilities accrue with rising age, and as function and the ability to sustain activity declines progressively with age, more elderly individuals will more often find participation too burdensome – yielding a successively more rarefied sample that is progressively more nonrepresentatively robust and healthy, compatible with the findings shown. Indeed, better health has been reported to influence self-selection for participation in studies in general[1], an observation that might be predicted to drive the finding observed, since health problems increase in prevalence with increasing age.

Factors driving self-selection for participation may vary depending on the character of the study. Although theoretical considerations suggest our findings may generalize broadly, other studies should evaluate how these findings are moderated based on the type of study and condition being examined.

One unsettling implication is that clinical guidelines lack a meaningful evidence basis, when applied to those of older age. Concerns have previously been expressed that when "evidence based" study findings *based on younger individuals* are implemented in elderly patients with comorbidities, via clinical practice guidelines reinforced by performance pay, this may result in perverse incentives that may diminish rather than enhance quality of care for elderly[34], by promoting promiscuous polypharmacy. Our findings suggest such concerns obtain even when recommendations derive from data actually procured in elderly participants. (Analogous concerns may -apply, irrespective of age, for patients with -multiple comorbidities, polypharmacy, dementia, disability, limited life expectancy, and/or past adverse responses to the recommended treatment – groups that, like elderly, often bear less favorable risk-benefit prospects.)

For older elderly, some have urged a more individualized "less is more" approach placing greater emphasis on clinical judgment, quality of life, and in-depth consultation with the patient and family[34-36]. This seems rational, given 1) absence of applicable evidence that medication benefits similarly apply, 2) increased medication burden, as age-related morbidities accrue, 3) amplified risk of drug adverse events, drug interactions and medication-taking errors in elderly with implications to quality of life and function, 4) magnified impact of added functional compromise in the elderly; coupled with 5) evidence, albeit non-randomized, suggesting striking subjective and objective benefits among elderly when systematic discontinuation of medications is undertaken[35 36].

In conclusion, as ~~subject~~ age advances, those who participate in clinical trials and observational studies may depart increasingly from those they are taken to represent~~, in physical activity and, likely, in health~~. That is, ~~r~~eal patients may depart increasingly from (an ever more rarefied, nonrepresentative, healthiest subsegment of) the elderly population that volunteers to participate in clinical studies~~trial subjects~~, rendering study findings of increasingly doubtful applicability. This magnifies concerns that, as the elderly swell as a fraction of the population, the~~, s~~~~. Our finding has fundamental implications for how results in elderly study participants may reflect on elderly more generally, implications which rise in importance as the population continues to age.~~~~.,~~~~, correspondingly larger disparities~~chasm may grow, between what is recommend~~ation~~ed based on “evidence,” and ~~treatment realities may~~ what is best for the patient. ~~be expected~~

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~~Both studies compared were designed to assess physical activity and health parameters in what can be defined as prevention, observational studies. The proven "lack of representativeness" would probably be even more significant in studies evaluating or comparing therapies for existing diseases.~~

~~Under representation of the elderly in clinical studies is a well accepted fact; several authors warn against automatic implementation of clinical practice guidelines (CPGs) based on EMB studies proving a positive benefit/risk ratio in younger adults, to the elderly. Boyd et al (Boyd) concluded that such implementation "could lead to inappropriate judgment of the care provided to older individuals,...create perverse incentives that emphasize the wrong aspects of care for this population and diminish the quality of their care". The present study further emphasizes that even when elders are included in studies, they do not represent the entire elderly population and we should be very cautious while interpreting the results. For most CPGs, EBM proving a positive benefit/risk ratio is lacking, in correlation to old age, co-morbidity, disability, dementia and limited life expectancy. For these rapidly increasing sub populations, it may be reasonable to adopt a completely different~~

~~, indiv~~

~~idualized, "less is more" approach as suggested by Garfinkel, while giving more place to clinical judgment, quality of life and in-depth consultation with the patient and family (Garfinkel 2010, Garfinkel 2007).~~

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Disclaimers

Competing Interest Statement: *All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that all authors have no relationships with any companies that might have an interest in the submitted work in the previous 3 years; nor do their spouses, partners, or children have any financial relationships that may be relevant to the submitted work; and none of the authors have any non-financial interests that may be relevant to the submitted work.*

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Author Contributions: Golomb was PI on the randomized trial, provided the concept, and generated the initial draft. Chan worked with Golomb to perform initial analyses and early revisions to the manuscript. Criqui was PI on the observational study, co-PI on the randomized trial, and provided access to the observational data. White provided senior statistical oversight and conceptual and editorial input. Evans conducted literature reviews on risk factors and worked with Golomb on an intermediate set of revisions. Koperski created Stata do-files, replicated the findings, reviewed all findings for correctness with Golomb, and performed editorial and administrative aspects of submission. All authors reviewed the manuscript for intellectual content.~~Dr. Golomb was PI on the randomized trial, had the idea, and generated the initial draft. Dr. Chan with Dr. Golomb performed initial analyses and early revisions to the manuscript. Dr. Criqui was PI on the observational study, co-PI on the randomized trial, and provided access to the observational data. Dr. White, study statistician, provided senior statistical oversight. Marcella Evans conducted literature reviews related to health predictors, and worked with Dr. Golomb to revise to the manuscript. Sabrina Koperski created Stata do-files for replication of findings, replicated the findings, reviewed all findings for correctness with Dr. Golomb, and performed the administrative aspects of submission. All authors reviewed the manuscript for intellectual content and provided conceptual and editorial input.All authors, external and internal, had full access to all of the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. The authors certify that this manuscript represents valid work and has not been published or is currently under consideration for publication elsewhere.~~

Data Sharing: Technical appendix, statistical code, and dataset available from the corresponding author (bgolomb@ucsd.edu).

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Table 1. Self-Rated "Relative Activity"* ~~Predicts~~ Relates to Health-Predictors ~~in Age > 50~~Those ~~Over~~ (Age >50)

Variable	Correlation Coefficient	P-value	Regression Coefficient, age adjusted†	P-value	*Age Relation, sign and P-value*
Times/wk exercise at least 20minutes	0.42	**<0.0001**	1.2 (0.092)	**<0.001**	*(-) 0.024*
CES-D (0-52)	-0.21	**<0.0001**	-1.3 (0.23)	**<0.001**	*NS*
Depressed (0-10)	-0.13	**0.0083**	-0.21 (0.086)	**0.017**	*NS*
Energy (0-10)	0.21	**<0.0001**	0.34 (0.064)	**<0.001**	*(+) 0.031*
Sleep problems (0-10)	-0.084	**0.028**	-0.21 (.095)	**0.024**	*NS*
Sleep quality (0-30)	0.078	**0.036**	0.037 (0.011)	**0.001**	*(+) 0.081*
Tired (0-10)	-0.29	**<0.0001**	-0.72 (0.13)	**<0.001**	*(+) 0.001*
Muscle weakness	-0.14	**<0.0001**	-0.29 (0.070)	**<0.001**	*(+) 0.005*
Fatigue w Exertion (0-10)	-0.26	**<0.0001**	-0.61 (0.12)	**<0.001**	*(+) 0.002*
Health (0-10)	0.20	**<0.0001**	0.31 (0.061)	**<0.001**	*(+) 0.071*
Satisfaction with health (0-100)	0.30	**<0.0001**	5.6 (0.69)	**<0.001**	*NS*
Glucose (mg/dL) ‡	-0.073	**0.049**	-0.73 (0.31)	**0.019**	*(+) 0.014*
HDL (mg/dL)	0.10	**0.0063**	1.2 (0.53)	**0.028**	*(+) 0.001*
Triglycerides (mg/dL)	-0.17	**<0.0001**	-10 (2.3)	**<0.001**	*NS*
Body mass index	-0.26	**<0.0001**	-0.97 (0.15)	**<0.001**	*(-) 0.002*
Waist (cm)	-0.23	**<0.0001**	-3.9 (0.63)	**<0.001**	*NS*
Platelets	-0.073	**0.051**	-2.7 (1.7)	**0.11**	*(-) 0.043*
White blood cell count	-0.08	**0.027**	-0.125 (0.050)	**+0.012**	*(+) 0.058*

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CES-D – Center for Epidemiological Studies -Depression scale~~y~~, HDL – high density lipoprotein cholesterol, NS – non-significant.

* Level of activity "compared to other persons your age" measured on a 5-point Likert scale: 1=much less active, 2=somewhat less active, 3=about as active, 4=somewhat more active, 5=much more active. ~~Relative Activity": self-rated physical activity relative to others ones age"~~

† Regression examines relative activity level relation to health predictor, among those age > 50, with age as an adjusted covariate in the regressions.
(The column to the far right gives the sign of the coefficient for the age variable, and its significance.)
‡ Note: patients with diabetes or measured glucose over 142 were excluded. This finding is thus despite range restriction.
Note that in these study ~~subjects~~participants, there is a "paradoxically" favorable age association for some variables that generally worsen with rising age, including energy, sleep quality, health, and HDL-cholesterol.

~~**Table 2. "Relative-Activity" Ratings*, by Age**~~

	Clinical Trial Sample		Observational Sample	
~~**Age Decade**~~	~~N~~	~~Relative Activity* Mean (SD)~~	~~N~~	~~Relative Activity* Mean (SD)~~
~~**30s**~~	~~80~~	~~3.35 (1.02)~~	~~34~~	~~3.26 (1.24)~~
~~**40s**~~	~~180~~	~~3.30 (1.20)~~	~~565~~	~~3.27 (1.23)~~
~~**50s**~~	~~308~~	~~3.49 (1.20)~~	~~650~~	~~3.68 (1.15)~~
~~**60s**~~	~~261~~	~~3.92 (1.07)~~	~~569~~	~~3.94 (1.05)~~
~~**70s**~~	~~151~~	~~3.89 (1.01)~~	~~512~~	~~3.97 (1.04)~~
~~**80s**~~	~~20~~	~~4.10 (1.07)~~	~~24~~	~~4.17 (1.31)~~
~~Significance of Change by Age Decade~~		~~P < 0.001~~		~~P < 0.001~~

~~N – Number; SD – Standard deviation~~

~~* Level of physical activity "compared to other persons your age" measured on a 5-point Likert scale: 1=much less active, 2=somewhat less active, 3=about as active, 4=somewhat more active, 5=much more active.~~

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Table 3. Older Participant Age Associated with Greater Self-reported "Relative-Activity", Ordinal Logit Analyses**

	Clinical Trial Sample				Observational Sample			
	Coefficient for Age Decade	Standard Error	pP-value	95% Confidence Interval	Coefficient for Age Decade	Standard Error	pP-value	95% Confidence Inter
Unadjusted	0.29	0.044	<0.001	0.21, 0.38	0.37	0.034	<0.001	0.31, 0.44
Multivariable adjusted‡	0.35	0.052	<0.001	0.25, 0.45	0.37	0.035	<0.001	0.30, 0.44

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Relative-Activity level (self-rated physical activity relative to others your age) was theas Level of activity "compared to other persons your age" measured on a 5-point Likert scale: 1=much less active, 2=somewhat less active, 3=about as active, 4=somewhat more active, 5=much more active. outcome, adjusted for age, gender, ethnicity, and education level.
‡Ordinal logit,

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Table ~~3~~2. "Relative-Activity" Ratings ~~Ratings~~*, by Age

		Clinical Trial Sample		Observational Sample
Age Decade	N	Relative Activity* Mean (SD)	N	Relative Activity* Mean (SD)
30s	80	3.35 (1.02)	34	3.26 (1.24)
40s	180	3.30 (1.20)	565	3.27 (1.23)
50s	308	3.49 (1.20)	650	3.68 (1.15)
60s	261	3.92 (1.07)	569	3.94 (1.05)
70s	151	3.89 (1.01)	512	3.97 (1.04)
80s	20	4.10 (1.07)	24	4.17 (1.31)
Significance of Change by Age Decade		P < 0.001		P < 0.001

N – Number; SD – Standard deviation
* Level of physical activity "compared to other persons your age" measured on a 5-point Likert scale: 1=much less active, 2=somewhat less active, 3=about as active, 4=somewhat more active, 5=much more active.

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Table 3. Older Participant Age Associated with Greater Self-reported "Relative-Activity"*, Ordinal Logit Analyses

	Clinical Trial Sample				Observational Sample			
	Coefficient for Age Decade	Standard Error	P-value	95% CI	Coefficient for Age Decade	Standard Error	P-value	95% CI
Unadjusted	0.29	0.044	<0.001	0.21, 0.38	0.37	0.034	<0.001	0.31, 0.44
Multivariable adjusted†	0.35	0.052	<0.001	0.25, 0.45	0.37	0.035	<0.001	0.30, 0.44

CI – Confidence interval
* Level of activity "compared to other persons your age" measured on a 5-point Likert scale: 1=much less active, 2=somewhat less active, 3=about as active, 4=somewhat more active, 5=much more active.
†Ordinal logit adjusted for age, gender, ethnicity, and education level.

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