PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Older the Better: Are Elderly Study Participants More Nonrepresentative?
AUTHORS	Golomb, Beatrice; Chan, Virginia; Evans, Marcella; Koperski, Sabrina; White, Halbert; Criqui, Michael

VERSION 1 - REVIEW

REVIEWER	Doron Garfinkel, M.D. Clinical Ass. Professor Head, Geriatric palliative department Shoham Geriatric Medical Center
REVIEW RETURNED	25-Aug-2012

THE STUDY	Page 6 Line 49 – 51: There is no consensus that white blood count represents an objective "health predictor", it may be affected by a variety of confounding factors and in my view, should not be included. The reference given (No.19. Brown et al.), refers only to coronary heart disease mortality and is therefore irrelevant to "health prediction". I suggest deleting the WBC parameter both here and in Table 3 (Page 17).
RESULTS & CONCLUSIONS	Results –Pg. 7-8 There seems to be complete confusion and mismatch between the text and Tables' numbers: Pg 7 Line 53 should be Table 3, not 1, on Page 8 – Table 2 should probably be Table 1, and Table 3 should be Table 2.
REPORTING & ETHICS	Older adults who volunteer to participate in clinical studies usually represent a healthier subpopulation and therefore are not representative of the entire elderly population. This bias is even more significant in those suffering from co-morbidity, disability, cognitive decline or limited life expectancy. The present manuscript contributes to previous studies stressing this point. The study design is good but suffers from some writing technical errors that need corrections. If these are corrected and some minor changes made, the manuscript is certainly worth publication. Specific comments: Pg 5 Line 25: What exactly do they mean by "non procreative"? Page 6 Line 49 – 51: There is no consensus that white blood count represents an objective "health predictor", it may be affected by a variety of confounding factors

	and in my view, should not be included. The reference given (No.19. Brown et al.), refers only to coronary heart disease mortality and is therefore irrelevant to "health prediction". I suggest deleting the WBC parameter both here and in Table 3 (Page 17). Results –Pg. 7-8 There seems to be complete confusion and mismatch between the text and Tables' numbers: Pg 7 Line 53 should be Table 3, not 1, on Page 8 – Table 2 should probably be Table 1, and Table 3 should be Table 2. Page 8 Line 6: The word "each" should be replaced by "both" Table 3 Page 17: CES-D is an abbreviation and should be clarified (Asterisk…) Glucose * - the asterisk does not match the caption below † Suggestions: 1). Below, I attach two abstracts relevant to the subject; in both the results are in agreement with those of the present study. I suggest the authors consider mentioning these 2 previous studies. 2). I suggest adding 2 short paragraphs at the end of the discussion, stressing the contribution of this study for improving future practical clinical decisions. I'll be happy if the authors and editor chose to accept it (with the references) as part of the manuscript, obviously with refinements and/or grammatical changes in line with their preferences. If this is not possible, please add these paragraphs with the references to my comments. The suggested additional paragraphs to the Discussion: 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, individualized, "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).

References

Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA. 2005;294(6):716-724.

Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults- Addressing Polypharmacy. Arch Int Med 170: 1648-54, 2010.

Garfinkel D, Zur-Gil S, Ben-Israel J. The war against Polypharmacy. A new, cost Effective, Geriatric - Palliative approach for improving drug therapy in disabled elderly people.
Isr Med Ass J 9: 430 - 4, 2007.

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Other references relevant to the subject that I suggest to include:

A). de Souto Barreto P, Ferrandez AM, Saliba-Serre B. Are Older Adults Who Volunteer to Participate in an Exercise Study Fitter and Healthier than Non-Volunteers? The participation bias of the study population. J Phys Act Health 2012, Jul 9. [Epub ahead of print]

CNRS UMR 6578 Laboratoire d'Anthropologie BioCulturelle, Université de la Méditerranée Aix-Marseille2, Marseille, PACA, France.

Abstract

BACKGROUND: Participation bias in exercise studies is poorly understood among older adults. This study was aimed at looking into whether older persons who volunteer to participate in an exercise study differ from non-volunteers.

METHODS: A self-reported questionnaire on physical activity and general health was mailed out to 1000 persons, aged 60 or over, who were covered by the medical insurance of the French National Education System. Among them, 535 answered it and sent it back. Two hundred and thirty-three persons (age 69.7 ±7.6, 65.7% women) said they would volunteer to participate in an exercise study and 270 (age 71.7 ±8.8, 62.2% women) did not.

RESULTS: Volunteers were younger and more educated than non-volunteers, but they did not differ in sex. They had less physical function decline and higher volumes of physical activity than non-volunteers. Compared to volunteers, non-volunteers had a worse self-reported health and suffered more frequently from chronic pain. Multiple logistic regressions showed that good self-reported health, absence of chronic pain, and lower levels of physical function decline were associated with volunteering to participate in an exercise study.

CONCLUSIONS: Volunteers were fitter and healthier than non-volunteers. Therefore, caution must be taken when generalizing the results of exercise intervention studies.

B). Nummela O, Sulander T, Helakorpi S, Haapola I, Uutela A, Heinonen H, Valve R, Fogelholm M. Register-based data indicated nonparticipation bias in a health study among aging people. J Clin Epidemiol 2011 Dec; 64(12):1418-25. Epub 2011 Jul 20.

Department of Lifestyle and Participation, National Institute for Health and Welfare (THL), Mannerheimintie 166, PO Box 30, FI-00271 Helsinki, Finland.

	olli.nummela@thl.fi Abstract OBJECTIVES: To examine nonparticipation in a survey by linking it with register information and identify potential nonresponse bias of inequalities in health status among aging people. STUDY DESIGN AND SETTING: Cross-sectional questionnaire survey with clinical checkups carried out in 2002 among persons born in 1926-1930, 1936-1940, and 1946-1950 in Southern Finland. The sample was linked with register information from Statistics Finland and analyzed in terms of participation and health status as measured by medicine reimbursements. RESULTS: Participation in the survey was more frequent among those who were older, female, married or cohabiting, higher educated and nonurban residents, and those with higher income and moderate health. Among nonrespondents, women were less healthy than men, whereas among respondents, the results were reversed. Among nonrespondents, better income was associated with unfavorable health. Poor health was generally more common among nonrespondents than respondents in several subgroups. CONCLUSION: Differences in response rates were found in sociodemographic factors, health, and socioeconomic position. Favorable health was generally more frequent among respondents than nonrespondents. In particular, health inequalities by gender and income differed between respondents and nonrespondents. Thus, nonresponse may lead to bias in analyses of health inequalities among aging people.
GENERAL COMMENTS	Older adults who volunteer to participate in clinical studies usually represent a healthier subpopulation and therefore are not representative of the entire elderly population. This bias is even more significant in those suffering from co-morbidity, disability, cognitive decline or limited life expectancy. The present manuscript contributes to previous studies stressing this point. The study design is good but suffers from some writing technical errors that need corrections. If these are corrected and some minor changes made, the manuscript is certainly worth publication. Specific comments: Pg 5 Line 25: What exactly do they mean by "non procreative"? Page 6 Line 49 – 51: There is no consensus that white blood count represents an objective "health predictor", it may be affected by a variety of confounding factors and in my view, should not be included. The reference given (No.19. Brown et al.), refers only to coronary heart disease mortality and is therefore irrelevant to "health prediction". I suggest deleting the WBC parameter both here and in Table 3 (Page 17). Results –Pg. 7-8 There seems to be complete confusion and mismatch between the text and Tables' numbers: Pg 7 Line 53 should be Table 3, not 1, on Page 8 – Table 2 should probably be Table 1, and Table 3 should be Table 2. Page 8 Line 6: The word "each" should be replaced by "both" Table 3 Page 17: CES-D is an abbreviation and should be clarified (Asterisk…) Glucose * - the asterisk does not match the caption below †

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	nonrespondents, women were less healthy than men, whereas among respondents, the results were reversed. Among nonrespondents, better income was associated with unfavorable health. Poor health was generally more common among nonrespondents than respondents in several subgroups. CONCLUSION: Differences in response rates were found in sociodemographic factors, health, and socioeconomic position. Favorable health was generally more frequent among respondents than nonrespondents. In particular, health inequalities by gender and income differed between respondents and nonrespondents. Thus, nonresponse may lead to bias in analyses of health inequalities among aging people. Doron Garfinkel, M.D. Clinical Ass. Professor Head, Geriatric palliative department Shoham Geriatric Medical Center

REVIEWER	Dr Dee Mangin Associate Professor Director Primary Care Research Unit Univeristy of Otago, Christchurch I have no conflict of interest to declare. I have met the primary author and impressed by her previous work.
REVIEW RETURNED	10-Sep-2012

THE STUDY	The study objective could be written to more tightly describe the study as: '....investigate whether age modifies such differences in terms of relative activity. Lines 46-48 p4 could do with clarifying - it is not clear until later in the methods exactly what relative-activity is. It might be more clear to say 'self-rated activity relative to....' Line 27 p6 Clarify that these were all baseline collected variables. Amongst the health predictor variables, were BP and smoking history collected for the RCT participants? These, in particular smoking history, could have an important relationship to exercise levels. P7 line 13 Outline why age 50 was chosen to define ‘older’ References: It would strengthen the study conclusions substantially to provide a reference to research outlining the link between actual measured and self reported (absolute) exercise levels. , and provide evidence that this is not a systematic response bias for both relative and reported actual activity levels (over-rating of both).
RESULTS & CONCLUSIONS	Minor suggestiosn for presentation P7 line 53

	This table 1 label does not match the sentence before it, which is about the relationship of self reported activity and multiple health predictors. The title of Table 3 could be more clearly written.
GENERAL COMMENTS	Overall I think the study was well done and provides some important information to add to the evidence base around and interpretation of clincial trials. (suggest clinical trials as an additional keyword). The suggestions I have made are mostly relatively minor points that I hope will help to improve the manuscript.

VERSION 1 – AUTHOR RESPONSE

C. Reviewer: I declare I have NO competing interests. Doron Garfinkel

1. Comment: Page 6 Line 49 – 51:
There is no consensus that white blood count represents an objective "health predictor", it may be affected by a variety of confounding factors and in my view, should not be included. The reference given (No.19. Brown et al.), refers only to coronary heart disease mortality and is therefore irrelevant to "health prediction". I suggest deleting the WBC parameter both here and in Table 3 (Page 17).

Reply: We have added citations to clarify that, while many of the studies examining WBC as an outcome- and mortality- predictor focus on the cardiovascular setting, prospective longitudinal studies have also identified it as an independent predictor of all-cause mortality (although, for the purpose of this paper, independence is not essential). We are sympathetic to concerns regarding confounding; but our focus is on whether factors are predictors of worse outcomes, without assertion that the relationship is causal. (Many predictors involve endogeneity, common cause, correlation with causal factors, and/or potential confounding.) We have added the citation for the Normative Aging Study and a larger prospective Korean study showing prospective all-cause mortality prediction by white blood cell count.

If the reviewer and editor still feel the concern has not been adequately addressed, we will remove reference to white blood cell count from text and tables.

de Labry LO, Campion EW, Glynn RJ, Vokonas PS. White blood cell count as a predictor of mortality: results over 18 years from the Normative Aging Study. J Clin Epidemiol 1990;43(2):153-7.
“The ubiquitous white blood cell count (WBC) has rarely been analyzed as a predictor of future mortality. We examined WBC measured in prospective examinations of 2011 initially healthy men in the Normative Aging Study (mean age 47.5), followed for an average of 13.6 years with 27,402 man-years of observation. Between 1970 and 1987, 183 participants died. Mortality rates for men with baseline WBC over 9000 were 12.2/1000 man-years, 1.8-2.5 times those of men with lower WBC in each of three age groups. Proportional hazards models controlling for established risk factors including age, systolic blood pressure, cholesterol and smoking status, found WBC at the baseline exam to be an independent predictor of mortality over the following years. Even within the normal

range, a difference of 1000 in the initial WBC increased the risk ratio by 1.2 (95% CI 1.1, 1.3). The relation of initial WBC to mortality was not affected by baseline age, body mass index (BMI), smoking or blood pressure. These findings are not explained by medication effects. We conclude that the WBC is an independent predictor of all-cause mortality."

Jee, S. H., J. Y. Park, et al. (2005). "White blood cell count and risk for all-cause, cardiovascular, and cancer mortality in a cohort of Koreans." Am J Epidemiol 162(11): 1062-9.
The authors conducted a 10-year prospective cohort study of mortality in relation to white blood cell counts of 437,454 Koreans, aged 40-95 years, who received health insurance from the National Health Insurance Corporation and were medically evaluated in 1993 or 1995, with white blood cell measurement. The main outcome measures were mortality from all causes, all cancers, and all atherosclerotic cardiovascular diseases (ASCVD). Hazard ratios and 95% confidence intervals were calculated using Cox proportional hazards models with adjustment for age and potential confounders. During follow-up, 48,757 deaths occurred, with 15,507 deaths from cancer and 11,676 from ASCVD. For men and women, white blood cell count was associated with all-cause mortality and ASCVD mortality but not with cancer mortality. In healthy nonsmokers, a graded association between a higher white blood cell count and a higher risk of ASCVD was observed in men (highest vs. lowest quintile: hazard ratio = 2.10, 95% confidence interval: 1.50, 2.94) and in women (hazard ratio = 1.35, 95% confidence interval: 1.17, 1.56). In healthy smokers, a graded association between a higher white blood cell count and a higher risk of ASCVD was also observed in men (highest vs. lowest quintile: hazard ratio = 1.46, 95% confidence interval: 1.25, 1.72). These findings indicate that the white blood cell count is an independent risk factor for all-cause mortality and for ASCVD mortality.

2. Comment: Results –Pg. 7-8
There seems to be complete confusion and mismatch between the text and Tables' numbers: Pg 7 Line 53 should be Table 3, not 1, on Page 8 – Table 2 should probably be Table 1, and Table 3 should be Table 2.

Reply: Thank you; We have corrected the order of the tables.

3. Comment: Older adults who volunteer to participate in clinical studies usually represent a healthier subpopulation and therefore are not representative of the entire elderly population. This bias is even more significant in those suffering from co-morbidity, disability, cognitive decline or limited life expectancy. The present manuscript contributes to previous studies stressing this point. The study design is good but suffers from some writing technical errors that need corrections. If these are corrected and some minor changes made, the manuscript is certainly worth publication.

Reply: Thank you for your kind comments and suggestions.

Specific comments:
4. Comment: Pg 5 Line 25:
What exactly do they mean by "non procreative"?

Reply: We have modified our text to be more clear. It now reads: "Participants were men over age

20 and surgically or chronologically postmenopausal women not on lipid medications…”

5. Comment: Page 6 Line 49 – 51:This comment is identical to the above, presumably added by the editors to their comments. See reply above.
There is no consensus that white blood count represents an objective "health predictor", it may be affected by a variety of confounding factors and in my view, should not be included. The reference given (No.19. Brown et al.), refers only to coronary heart disease mortality and is therefore irrelevant to "health prediction". I suggest deleting the WBC parameter both here and in Table 3 (Page 17).

6. Comment: Page 8 Line 6:
The word "each" should be replaced by "both"

Reply: Done. The sentence now reads: “This was true in both the clinical trial sample and the observational study sample”

7. Comment: Table 3 Page 17:
CES-D is an abbreviation and should be clarified (Asterisk…)

Glucose * - the asterisk does not match the caption below †

Reply: We have defined the abbreviations, and corrected the symbols.

Suggestions:
8. Comment: 1). Below, I attach two abstracts relevant to the subject; in both the results are in agreement with those of the present study. I suggest the authors consider mentioning these 2 previous studies.

Reply: Thank you for bringing these articles to our attention.

9. Comment: 2). I suggest adding 2 short paragraphs at the end of the discussion, stressing the contribution of this study for improving future practical clinical decisions.

I'll be happy if the authors and editor accept it (with the references) as part of the manuscript, obviously with refinements and/or grammatical changes in line with their preferences.
If this is not possible, please add these paragraphs with the references to my comments.

The suggested additional paragraphs to the Discussion:

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, individualized, "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).

Reply:
These are wonderful points, and we greatly appreciated the suggestion of text and the option to use it (and the emphasis elsewhere in reviewer comments that we understated the implications). We didn't feel proper taking text wholesale, but text has been added to the discussion to reflect these considerations, and to try to better stress the implications of these findings.

The two paragraphs we have added are as follows:
"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 elderly34, 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 family34-36. 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 undertaken35 36."

We have also modified the final paragraph to read:
"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.”

References

Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA. 2005;294(6):716-724.

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CNRS UMR 6578 Laboratoire d'Anthropologie BioCulturelle, Université de la Méditerranée Aix-Marseille2, Marseille, PACA, France.
Abstract
BACKGROUND: Participation bias in exercise studies is poorly understood among older adults. This study was aimed at looking into whether older persons who volunteer to participate in an exercise study differ from non-volunteers.
METHODS: A self-reported questionnaire on physical activity and general health was mailed out to 1000 persons, aged 60 or over, who were covered by the medical insurance of the French National Education System. Among them, 535 answered it and sent it back. Two hundred and thirty-three persons (age 69.7 ±7.6, 65.7% women) said they would volunteer to participate in an exercise study and 270 (age 71.7 ±8.8, 62.2% women) did not.
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CONCLUSIONS: Volunteers were fitter and healthier than non-volunteers. Therefore, caution must be taken when generalizing the results of exercise intervention studies.

B). Nummela O, Sulander T, Helakorpi S, Haapola I, Uutela A, Heinonen H, Valve R, Fogelholm M. Register-based data indicated nonparticipation bias in a health study among aging people. J Clin Epidemiol 2011 Dec; 64(12):1418-25. Epub 2011 Jul 20.

Department of Lifestyle and Participation, National Institute for Health and Welfare (THL), Mannerheimintie 166, PO Box 30, FI-00271 Helsinki, Finland. olli.nummela@thl.fi

Abstract

OBJECTIVES: To examine nonparticipation in a survey by linking it with register information and identify potential nonresponse bias of inequalities in health status among aging people.

STUDY DESIGN AND SETTING: Cross-sectional questionnaire survey with clinical checkups carried out in 2002 among persons born in 1926-1930, 1936-1940, and 1946-1950 in Southern Finland. The sample was linked with register information from Statistics Finland and analyzed in terms of participation and health status as measured by medicine reimbursements.

RESULTS: Participation in the survey was more frequent among those who were older, female, married or cohabiting, higher educated and nonurban residents, and those with higher income and moderate health. Among nonrespondents, women were less healthy than men, whereas among respondents, the results were reversed. Among nonrespondents, better income was associated with unfavorable health. Poor health was generally more common among nonrespondents than respondents in several subgroups.

CONCLUSION: Differences in response rates were found in sociodemographic factors, health, and socioeconomic position. Favorable health was generally more frequent among respondents than nonrespondents. In particular, health inequalities by gender and income differed between respondents and nonrespondents. Thus, nonresponse may lead to bias in analyses of health inequalities among aging people.

Reply: We greatly appreciate the additional important citations and have incorporated them into the manuscript.

Doron Garfinkel, M.D.
Clinical Ass. Professor
Head, Geriatric palliative department
Shoham Geriatric Medical Center
Parsed Hana, Israel 37000

Reviewer: Dr Dee Mangin
Associate Professor
Director Primary Care Research Unit
Univeristy of Otago, Christchurch

I have no conflict of interest to declare.
I have met the primary author and impressed by her previous work.

Comment: The study objective could be written to more tightly describe the study as: '....investigate whether age modifies such differences in terms of relative activity.

Reply: Thank you for the suggested wording, which we have adapted. “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.”

Comment: Lines 46-48 p4 could do with clarifying - it is not clear until later in the methods exactly what relative-activity is.
It might be more clear to say 'self-rated activity relative to....'

Reply: That is an excellent point and we have sought to add clarity. We were unsuccessful in identifying wording that was self-evident in its meaning. Adding the words “relative to others your age” proved confusing in sentences in which we mentioned this was assessed by age.

The abstract we have added “i.e.” in “Design: Cross-sectional examination of the relation of participant age to reported “relative activity” (i.e. compared to others of the same age)”

The text now reads “Subjects 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.””

We have adjusted titles of Tables in an effort to clarify

Comment: Line 27 p6 Clarify that these were all baseline collected variables.

Reply: Done. Methods now state: “All variables were assessed at baseline (prior to study treatment).”

Comment: Amongst the health predictor variables, were BP and smoking history collected for the RCT participants? These, in particular smoking history, could have an important relationship to exercise levels.

Reply: These are good points.
Smoking history was collected, but few subjects in the study were smokers (only 8%), providing for very low power to look at relationships in this sample.
SBP was measured, but the relation of SBP to activity-relative-to-others-ones-age did not reach significance, perhaps because it has bidirectional associations to exercise: those with low SBP can have reduced vigor due to reduced perfusion pressure (particularly where low SBP derives from systolic dysfunction); and those who don’t exercise may have higher blood pressure. The relationship was strongest excluding those with BP under 100mmHg, but still did not meet significance.

Comment: P7 line 13 Outline why age 50 was chosen to define 'older'.

Reply: We have added the text "(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.)" Starting in the 50s a stronger difference in relative activity is evident, so it was this group in whom there was primary interest in the relation of relative activity to other predictors.

Comment: References: It would strengthen the study conclusions substantially to provide a reference to research outlining the link between actual measured and self reported (absolute) exercise levels. , and provide evidence that this is not a systematic response bias for both relative and reported actual activity levels (over-rating of both).

Reply: We have added this text:
"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."

Minor suggestions for presentation
Comment: P7 line 53
This table 1 label does not match the sentence before it, which is about the relationship of self reported activity and multiple health predictors.

Reply: Thank you for noting this; we have corrected the table order.

Comment: The title of Table 3 could be more clearly written.

Reply: We have modified the table title (now table 1).
Self-Rated "Relative Activity"* Relates to Health-Predictors (Age >50)
** 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.

Comment: Overall I think the study was well done and provides some important information to add to the evidence base around and interpretation of clincial trials. (suggest clinical trials as an additional keyword). The suggestions I have made are mostly relatively minor points that I hope will help to improve the manuscript.

Reply: We have added the key word "clinical trials."

VERSION 2 – REVIEW

REVIEWER	Doron Garfinkel, M.D., Clinical Ass. Professor Head, Geriatric Palliative Department Shoham Geriatric Medical Center I have NO conflict of interest
REVIEW RETURNED	04-Nov-2012

GENERAL COMMENTS	An original, well designed important research that contributes much to our increasing body of evidence indicating that we must not rely on traditional clinical research perceptions when elderly people are involved. Age related heterogeneity is too extensive making any "single model clinical practice guideline" inappropriate for most, if not all, sub-populations of elderly people.