

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Effects of statin medication on mortality risk associated with type 2 diabetes in older persons The population-based AGES-Reykjavik Study
<b>AUTHORS</b>	Olafsdottir, Elin; Aspelund, Thor; Sigurdsson, Gunnar; Thorsson, Bolli; Eiriksdottir, Gudny; Harris, Tamara; Launer, Lenore; Benediktsson, Rafn; Gudnason, Vilmundur

### VERSION 1 - REVIEW

<b>REVIEWER</b>	<i>Peter M Nilsson, Professor</i> Department of Clinical Sciences Lund University University Hospital S-205 02 Malmö SWEDEN
<b>REVIEW RETURNED</b>	01-May-2011

<b>GENERAL COMMENTS</b>	<p>This was a large observational study on the benefits of statin treatment in elderly patients with or without diabetes from Reykjavik, Iceland. The authors have fulfilled the criteria for observational papers as presented in the STROBE check-list from 2007 (attachment).</p> <p>I have the following questions and comments to the authors:</p> <ol style="list-style-type: none"><li>1. The cohort had a very high mean age (77 years) and were followed for 5.3 years. This means that they could have been health-selected already from the start. This should be commented upon.</li><li>2. A diagnosis of diabetes was based on, besides self-report or use of anti-diabetes drugs, a single fasting serum glucose level. This is suboptimal for a true diagnosis when repeated samples should be used, why this fact should be commented upon.</li><li>3. The follow-up period was stated to be 5.3 years, but I cannot see in the text when the final follow-up date was.</li><li>4. It is strange to notice in Table 1 that current sports was practiced by 40-50% of these elderly subjects. Is this an accurate description or not? Please clarify.</li><li>5. In every observational study so called rest confounding could influence and bias the results. It is well-known that adverse social factors could negatively impact on outcomes as well as drug treatment patters. Do the authors have data to show that no social selection bias could explain the more favourable outcome in patients on statins as compared to patients not on statins? Are variables such as educational level or income available?</li></ol>
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<b>REVIEWER</b>	<b>Gang Hu, MD, MPH, PhD</b> Assistant Professor, Chronic Disease Epidemiology Population Science Pennington Biomedical Research Center 6400 Perkins Road Baton Rouge, Louisiana 70808
<b>REVIEW RETURNED</b>	02-May-2011

<b>GENERAL COMMENTS</b>	<p>This manuscript examined association of statin medication on total and cardiovascular disease mortality among people with and without a history of type 2 diabetes and coronary heart disease in the population-based Age, Gene/Environment Susceptibility (AGES)-Reykjavik study. The material is suitable, the data collection seems to be adequate, statistical analyses are appropriate and the paper is well written. I suggest that this manuscript can be reconsidered with revision.</p> <ol style="list-style-type: none"> <li>1. More details are needed about the validity of death register.</li> <li>2. Education, exercise, and dietary factors may be associated with the mortality risk. Are these data available in your study? If not, this limitation should be mentioned.</li> </ol>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: Peter M Nilsson, Professor  
Department of Clinical Sciences  
Lund University  
University Hospital  
S-205 02 Malmö  
SWEDEN

This was a large observational study on the benefits of statin treatment in elderly patients with or without diabetes from Reykjavik, Iceland. The authors have fulfilled the criteria for observational papers as presented in the STROBE check-list from 2007 (attachment).

I have the following questions and comments to the authors:

1. The cohort had a very high mean age (77 years) and were followed for 5.3 years. This means that they could have been health-selected already from the start. This should be commented upon.  
Authors' response: We have put greater emphasis on this point in the limitations of the study (changes in bold). It now reads: "A limitation is the non-attendance of frail individuals in the study that may cause a possible bias towards more healthy individuals at baseline of this study."

2. A diagnosis of diabetes was based on, besides self-report or use of anti-diabetes drugs, a single fasting serum glucose level. This is suboptimal for a true diagnosis when repeated samples should be used, why this fact should be commented upon.  
Authors' response: Our definition is a standard epidemiology definition where no further examination such as oral glucose tolerance test for diagnosis of type 2 diabetes is carried out on individuals. A sentence to this effect has been put in the limitation section. "A limitation is the lack of glucose tolerance test for diagnosis of diabetes."

3. The follow-up period was stated to be 5.3 years, but I cannot see in the text when the final follow-

up date was.

Authors' response: On page 6 line 29 we have added "until end of 2009". The sentence now reads: "In the present study 5152 of these survivors are included, with a mean age of 77 years (range 66-96) and a median follow up time of 5.3 years until end of 2009."

4. It is strange to notice in Table 1 that current sports was practiced by 40-50% of these elderly subjects. Is this an accurate description or not? Please clarify.

Authors' response: We thank the reviewer for pointing this out. Using current sports terminology was a mistake on our side as it is too narrow a description of the questions participants were asked. The questions were about leisure time physical activity both current and in midlife and an indicator of occasional or more frequent participation in moderate or vigorous physical activity. We have changed the terminology accordingly in Table 1 and added a new line with current physical activity as well as a description in the methods section page 7 line 30 to this effect: "Participants answered questions about frequency of moderate or vigorous physical activity, both current and in midlife. Answers were categorized into never, rarely, occasionally, moderate or high frequency of participation. In this study a binary variable for physical activity was used as an indicator for occasional or higher frequency of participation versus never or rarely participating."

5. In every observational study so called rest confounding could influence and bias the results. It is well-known that adverse social factors could negatively impact on outcomes as well as drug treatment patters. Do the authors have data to show that no social selection bias could explain that more favourable outcome in patients on statins as compared to patients not on statins? Are variables such as educational level or income available?

Authors' response: We thank the reviewer for this important comment. We have information on educational level of the participants and this has now been added as a new line in Table 1. A description of educational level categories has also been added to the methods section following the description on physical activity. "Answers about education were categorized into a binary variable: higher than secondary education versus secondary education or less." We have added analyses adjusting for educational level as well as physical activity and this did not have any material effect on the results as can be seen in the Supplement Figure 3 that has also been added. We added the following sentence in the results section , page 10 line 53: "An additional analysis of mortality rates with adjustment for current physical activity and education level did not have any material effect on the results or the conclusions drawn from the data. The additionally adjusted mortality rates are shown in Supplement Figure 3."

Reviewer: Gang Hu, MD, MPH, PhD

Assistant Professor, Chronic Disease Epidemiology Population Science Pennington Biomedical Research Center 6400 Perkins Road Baton Rouge, Louisiana 7080

This manuscript examined association of statin medication on total and cardiovascular disease mortality among people with and without a history of type 2 diabetes and coronary heart disease in the population-based Age, Gene/Environment Susceptibility (AGES)-Reykjavik study. The material is suitable, the data collection seems to be adequate, statistical analyses are appropriate and the paper is well written. I have two comments that need to be addressed.

1. More details are needed about the validity of death register.

Authors' response: The national registry on mortality is an adjudicated registry. This has now been added to the description on page 7 line 32 and we have included in the text a website address to a

description of the registry. <http://www.statice.is/Statistics/Population/Births-and-deaths>

2. Education, exercise, and dietary factors may be associated with the mortality risk. Are these data available in your study? If not, this limitation should be mentioned.

Authors' response: Educational level has now been added to the analysis, as explained in response to comment 5 above. Physical activity including exercise has also been added to the analysis as can be seen in response 4 above. Dietary information is not available for this analysis. A sentence to that effect has been added to limitations description. "A limitation is the unavailability of dietary information for this analysis."

Further revision:

On page 10 line 37 we made a correction where we added the word cardiovascular. The sentence now reads:

Statin use was associated with 16% (-24% to 43%) lower cardiovascular mortality rate in individuals without diabetes as shown in Figure 1, albeit not statistically significant.

#### VERSION 2 - REVIEW

<b>REVIEWER</b>	<b><i>Peter Nilsson</i></b>
<b>REVIEW RETURNED</b>	20-May-2011

<b>GENERAL COMMENTS</b>	The authors have answered the queries that I raised. Please notice that I did NOT ask for OGTT data (point 2 from me) but raised the comment that more than one elevated fasting glucose sample separated in time is normally needed to establish a diagnosis of type 2 diabetes according to modern guidelines. OGTT is nice to have but not necessary according to guidelines.
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