

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Clinical outcome of nonalcoholic fatty liver disease: an eleven-year follow-up study
AUTHORS	Tang, Xiaoping; Shi, Yanyan; Du, Juan; Hu, Keming; Zhou, Tingting; Chen, Lan; Zhang, Yanming; Li, Fujun; Zhang, Huier; Liebe, Roman; Meyer, Christoph; Dooley, Steven; Zhu, Zhongwei; Weng, Hong-Lei; JIA, Jinzhu; Huang, Tong

VERSION 1 – REVIEW

REVIEWER	Giovanni Tarantino Federico II University Medical School, ClinandExpert Medicine
REVIEW RETURNED	02-Dec-2021

GENERAL COMMENTS	<p>Authors state that....Metabolic syndrome such as diabetes, hypertension and hyperuricemia are the main "consequences" of NAFLD.....letting understand that there could be a cause-and-effect relationship or at least a temporal association that should be better elucidated to avoid misleading take-home message (concomitant, during the course or tardy?....</p> <p>There is plenty of evidence that metabolic syndrome, type 2 diabetes mellitus are determinant risk factors for the onset/progression of NAFLD.</p> <p>Thus, authors should point out, commenting at large this aspect, and dig into co-factors that might mediate the presence of both NAFLD and extra-hepatic diseases.</p> <p>There is one paper of Alexander that should be better quoted in the sense that authors evidenced thatCardiovascular risk assessment in adults with a diagnosis of NAFLD is important but should be done in the same way as for the general population. https://doi.org/10.1136/bmj.l5367</p> <p>On the other hand, two of the direct risk factors for NAFLD, interestingly found in this study, are BMI and Triglycerides.....but, aren't they two key factors of the metabolic syndrome?</p> <p>Authors have found that diet and exercise are two main factors impacting on progression of NAFLD.</p> <p>Thus, authors have honestly recognised that life-style modifications have determined the difference from previously reported data on evolution of NAFLD.</p> <p>But, there is a bias in their study, not a negative section bias in other studies.</p>
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REVIEWER	Ghazala Kaukab Raja Pir Mehr Ali Shah Arid Agr Univ Rawalpindi
REVIEW RETURNED	13-Dec-2021

GENERAL COMMENTS	Quality of figure 2 needs to be improved as it was not clear/readable In Results section Line Nos 31-33 the sentence is confusing “15 (in 2006) and 16 (in 2016) over-weighted women aged less than 30 years, the NAFLD prevalence was 20% and 43.8%, respectively”
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Prof. Giovanni Tarantino, Federico II University Medical School

Comments to the Author:

Authors state that...Metabolic syndrome such as diabetes, hypertension and hyperuricemia are the main "consequences" of NAFLD.

....letting understand that there could be a cause-and-effect relationship or at least a temporal association that should be better elucidated to avoid misleading take-home message (concomitant, during the course or tardy?....

Answer: Thanks for the good suggestion. We discuss this issue in the revised manuscript (page 11):

“An important issue is the cause-and-effect relationship between NAFLD and its clinical outcomes such as diabetes, hypertension and hyperuricemia. A dynamic Bayesian network in the current study provides direct evidence in this issue: NAFLD directly results in alterations of several parameters, including DBp, SBp and UA, suggesting that NAFLD directly contributes to the occurrence of hypertension and hyperuricemia. The underlying mechanisms require further investigation”.

There is plenty of evidence that metabolic syndrome, type 2 diabetes mellitus are determinant risk factors for the onset/progression of NAFLD. Thus, authors should point out, commenting at large this aspect, and dig into co-factors that might mediate the presence of both NAFLD and extra-hepatic diseases.

Answer: Thanks for this important suggestion. We discuss this issue in the revised manuscript (page 11):

“The current dynamic Bayesian network analysis does not confirm a direct cause-and-effect relationship between NAFLD and type 2 diabetes mellitus. There are plenty of studies showing the close relationship between type 2 diabetes and NAFLD [20]. Pathophysiologically, insulin resistance is a key event in both NAFLD and diabetes progression [20]. However, genome-wide association studies have not yet identified the exact impact of insulin resistance on the variants associated with NAFLD severity [20,21]. Clarification of the cause-and-effect relationship between NAFLD and diabetes requires further long-term follow-up studies.”

There is one paper of Alexander that should be better quoted in the sense that authors evidenced thatCardiovascular risk assessment in adults with a diagnosis of NAFLD is important but should be done in the same way as for the general population. <https://doi.org/10.1136/bmj.l5367>

Answer: Thanks for the suggestion. We have cited and discussed the literature in the revised manuscript (page 10-11).

“Whether NAFLD is associated with the risk of severe heart or brain diseases such as acute myocardial infarction (AMI) and stroke is worth further investigation. A recent matched cohort study analyzed databases from four European countries, which included 17.7 million patients with NAFLD or NASH [19]. These patients had a mean follow-up of 2.1 to 5.5 years. The study showed that the diagnosis of NAFLD appears not to be associated with AMI or stroke risk after adjustment for established cardiovascular risk factors. Nevertheless, the authors mentioned that cardiovascular risk assessment in adults with a diagnosis of NAFLD is important [19]. Follow-up for 5 years might be not sufficient to reach a conclusion for this issue.”.

On the other hand, two of the direct risk factors for NAFLD, interestingly found in this study, are BMI and Triglycerides.....but, aren't they two key factors of the metabolic syndrome?

Answer: Yes, both BMI and triglycerides are key factors of the metabolic syndrome.

Authors have found that diet and exercise are two main factors impacting on progression of NAFLD. Thus, authors have honestly recognised that life-style modifications have determined the difference from previously reported data on evolution of NAFLD. But, there is a bias in their study, not a negative section bias in other studies.

Answer: We agree with the reviewer. Diet and exercise are two main factors impacting progression of NAFLD. As a retrospective study, we did not obtain complete information relevant to diet and exercise of the examined population. We are performing a prospective follow-up study to clarify the impact of diet and exercise in NAFLD progress.

Reviewer: 2

Dr. Ghazala Kaukab Raja, Pir Mehr Ali Shah Arid Agr Univ Rawalpindi

Comments to the Author:

Quality of figure 2 needs to be improved as it was not clear/readable

Answer: We have provided a new Figure 2 in the revised manuscript.

In Results section Line Nos 31-33 the sentence is confusing “15 (in 2006) and 16 (in 2016) overweighted women aged less than 30 years, the NAFLD prevalence was 20% and 43.8%, respectively”.

Answer: Sorry for the confusion. We have changed the sentences to:

“In 2006, there were 15 overweight women aged less than 30 years. Among them, 3 presented as NAFLD (20%). In 2016, 7 out of 16 overweight women aged less than 30 years were identified. The NALFD prevalence had increased to 43.8% (Supplementary Table 3)”.

VERSION 2 – REVIEW

REVIEWER	Giovanni Tarantino Federico II University Medical School, ClinandExpert Medicine
REVIEW RETURNED	18-Mar-2022

GENERAL COMMENTS	For the love of precision, authors should correctly quoted the work of Alexander and coll. that is....BMJ 2019; 367 doi: https://doi.org/10.1136/bmj.l5367 (Published 08 October 2019) Cite this as: BMJ 2019;367:l5367...whose conclusions areThe diagnosis of NAFLD in current routine care of 17.7 million patient appears not to be associated with AMI or stroke risk after adjustment for established cardiovascular risk factors. Cardiovascular risk assessment in adults with a diagnosis of NAFLD is important but..... should be done in the same way as for the general population.
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REVIEWER	Ghazala Kaukab Raja Pir Mehr Ali Shah Arid Agr Univ Rawalpindi
REVIEW RETURNED	01-Apr-2022

GENERAL COMMENTS	Manuscript indicates Figure 2A, Figure 2B and Figure 2C in the written text but actual Figure 2C is missing.
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Prof. Giovanni Tarantino, Federico II University Medical School

Comments to the Author:

For the love of precision, authors should correctly quoted the work of Alexander and coll. that is....BMJ 2019; 367 doi: <https://doi.org/10.1136/bmj.l5367> (Published 08 October 2019)

Cite this as: BMJ 2019;367:l5367...whose conclusions areThe diagnosis of NAFLD in current routine care of 17.7 million patient appears not to be associated with AMI or stroke risk after adjustment for established cardiovascular risk factors. Cardiovascular risk assessment in adults with a diagnosis of NAFLD is important but..... should be done in the same way as for the general population.

Answer: We thank the reviewer for the comment. We have corrected the citations as suggested.

Reviewer: 2

Dr. Ghazala Kaukab Raja, Pir Mehr Ali Shah Arid Agr Univ Rawalpindi

Comments to the Author:

Manuscript indicates Figure 2A, Figure 2B and Figure 2C in the written text but actual Figure 2C is missing.

Answer: We thank the reviewer for being very careful in the analysis of our manuscript and are sorry for the mistake. We have provided a corrected Figure 2 in the revised manuscript.