

## Author's response to reviews

**Title:** Agrarian diet and diseases of affluence - Do evolutionary novel dietary lectins cause leptin resistance?

### Authors:

Tommy Jonsson ([Tommy.Jonsson@med.lu.se](mailto:Tommy.Jonsson@med.lu.se))  
Stefan Olsson ([stefan.olsson@ecol.kvl.dk](mailto:stefan.olsson@ecol.kvl.dk))  
Bo Ahren ([Bo.Ahren@med.lu.se](mailto:Bo.Ahren@med.lu.se))  
Thorkild C Bog-Hansen ([tcbh@plab.ku.dk](mailto:tcbh@plab.ku.dk))  
Anita Dole ([Anita@plab.ku.dk](mailto:Anita@plab.ku.dk))  
Staffan Lindeberg ([staffan.lindeberg@med.lu.se](mailto:staffan.lindeberg@med.lu.se))

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### Author's response to reviews:

Cover letter - first revision

Agrarian diet and diseases of affluence

- Do evolutionary novel dietary lectins cause leptin resistance?

The paper has been formatted according to the manuscript formatting checklist.

Reviewer: Oreste Gualillo

A strong reduction in the ms should be done. The article is intriguing but too long for an "Hypothesis" format. Speculations should be avoided. The first part of the article should be significantly reduced whereas: presentation, testing and implications should be enlarged and supported by experimental evidences.

The paper has been shortened considerably and speculations have been avoided, whereas presentation, testing and implications have been enlarged and supported by experimental evidences when possible.

Reviewer: Rob M. van Dam

1. The authors state that the global pattern of diseases of affluence suggests that some environmental factor among agricultural societies could initiate these diseases.

However, they provide very few concrete examples that support that statement (Trobriand Islanders, Parkateje), and one example that does not support their statement (Amondava). The prevalence of diseases such as obesity and type 2 diabetes is strongly associated with increasing westernization and urbanization, but prevalence is very low in many poor agricultural communities. Thus, if the authors cannot provide stronger evidence for their statement, this seems to undermine most of their rationale for the hypothesis.

We have substantially rewritten the section on Global epidemiologic pattern to clarify our argument, and also incorporated comments on the association between some diseases of affluence, westernization and urbanization. More examples to support our statement have been added.

2. There will be many differences in diet between agricultural and non-agricultural populations; there are many biologically active components of grains, and many genes with a similar evolutionary history to leptin that potentially affect disease-related pathways. Moreover, there does not seem to be any data that shows that lectins affect the leptin receptor (in contrast to what the last sentence and the title of the section on lectin interaction with leptin suggest). Wouldn't such data be necessary before considering the proposed lectin-leptin receptor pathway an interesting candidate for explaining patterns of 'diseases of affluence'?

The text has been changed where appropriate to account for the existence of alternatives to our proposals of cereal diet, leptin and lectin as factors related to diseases of affluence. The text now also emphasizes the properties of these factors which cause us to propose them.

3. Several epidemiological cohort studies have examined the association between grain consumption and weight change and risk of type 2 diabetes. These do not suggest that higher grain consumption increases risk of obesity and type 2 diabetes. In contrast, whole grain consumption was associated with a lower risk of these conditions and increased insulin sensitivity in one randomized intervention study in humans. The authors should address this issue.

This issue has been addressed in the section Testing the hypothesis.

4. The statement that 'The notion that dietary lectins could inhibit binding implies that leptin binding affinity should be lower in leptin resistant humans on an agricultural diet' (Section on implications of the hypothesis) is not correct. Leptin binding affinity is per definition lower in leptin resistant humans. Thus, the observation that the proportion of unbound leptin is increased in obese humans does not provide support for a relation with agrarian diets. Information on associations between diet and leptin levels seems highly relevant for the postulated hypothesis, but is only very briefly and incompletely referred to in the paper.

The term leptin resistance is, in our understanding, not defined as a lower leptin binding affinity. The term is used to refer to the mechanistically unexplained clinical observation that peripheral administration of exogenous leptin does not promote satiation and weight loss in some animal models and most obese humans [1]. In contrast, offered explanations for this observation has ranged from impaired transport of leptin across the blood-brain barrier and post-receptor effects of leptin on the hypothalamic energy expenditure network [1]. We therefore stand by our proposed notion on dietary lectins possible inhibition of leptin binding and its implications on bound leptin proportions.

The brevity of references on associations between diet and leptin levels is due to the overall scarcity of such studies, and in particular studies comparing agrarian and non-agrarian diets.

5. Although the paper contains interesting information on for example molecular evolution, the texts with general background information are much too long for the particular aims of a hypothesis paper of this type. The authors can refer to other publications for readers who are not familiar with the general principles.

General background information has been replaced by appropriate references.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Because intervention studies are prospective one tests the effect of an intervention on the incidence (not prevalence) of a disease (Abstract, 'testing the hypothesis').

Abstract has been corrected.

## References

1. El-Haschimi K, Lehnert H: Leptin resistance - or why leptin fails to work in obesity. *Exp Clin Endocrinol Diabetes* 2003, 111:2-7.