

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	High prevalence of underweight and under-nutrition in Japanese inpatients with schizophrenia: a nationwide survey
AUTHORS	Sugai, Takuro; Suzuki, Yutaro; Yamazaki, Manabu; Shimoda, Kazutaka; Mori, Takao; Ozeki, Yuji; Matsuda, Hiroshi; Sugawara, Norio; Yasui-Furukori, Norio; Minami, Yoshitake; Okamoto, Kurefu; Sagae, Toyoaki; Someya, Toshiyuki

VERSION 1 - REVIEW

REVIEWER	Manuel Gurpegui University of Granada, Granada, Spain
REVIEW RETURNED	22-Jul-2015

GENERAL COMMENTS	<p>1) THIS MANUSCRIPT compares the body mass index (BMI) of 15461 schizophrenia inpatients with the BMI of 7655 schizophrenia outpatients and the general population in Japan. The study is based on a nationwide sample with participating institutions that are members of the Japan Psychiatric Hospital Association. This huge sample makes this report particularly valuable and is worth publishing. The study includes other variables such as lipid and fasting glucose levels, blood pressure and daily smoking rate. In contrast with European or North American schizophrenia patients (see refs. 3 and 4), persons suffering from schizophrenia (especially inpatients) in Japan are characterized by lower BMI.</p> <p>2) However, before accepting this manuscript for publication, SOME IMPROVEMENTS are needed:</p> <ul style="list-style-type: none"> a) Please report response rates both among institutions and within institutions (in the Study participants section of the Methods section as well as in Figure 1). b) Please report separately Overweight and Obesity (in both Figure 1 and Table 3), in order to make it possible to compare with other studies on overweight and obesity among schizophrenia patients. c) Give the literature reference for the values employed to calculate the chlorpromazine equivalents (Methods section). d) Please give account of the prevalence rates of current daily smoking, hypertension and diabetes mellitus in the Japanese general population, in order to be able to compare them with data of Tables 1 and 3. e) Please analyze the possible association of daily smoking with BMI
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	<p>and type and dose of antipsychotic medication.</p> <p>f) Please comment, in the Discussion section, on the lower rates of hypertension and diabetes mellitus among inpatients and their potential health advantage, in contrast with the disadvantage attributed to underweight among these individuals.</p>
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REVIEWER	Arleen Rowell St Andrews Healthcare, Cliftonville Northampton, England NN1 5DG
REVIEW RETURNED	29-Jul-2015

GENERAL COMMENTS	<p>Thank you for this paper and there is valuable information included, specifically to highlight scale of nutritional risk for this vulnerable group of patients. This of course is a precursor to being able to address what has been identified as a significant health risk. Please see my further comments below.</p> <p>3. Study design:-</p> <p>While there is no universally accepted definition for undernutrition, the biochemical parameters given in this study are not the indicators for under nutrition typically used in clinical practice; at least one indicator of protein status is invariably included, and also micronutrients such as iron. Note the paper Suzuki et al included hypoproteinemia. If this study had access to only those biochemical parameters given, and perhaps taken from an existing data set, that should have been made clear as a study limitation and highlighted as a point for further investigation.</p> <p>Blood cholesterol levels – it's helpful to state that these tend to decrease with increasing age (the inpatients were significantly older than outpatients) and while low cholesterol levels are associated with increased mortality, some studies have identified that low cholesterol is associated with other markers of decreased health, including weight loss , low serum albumin, reduced functional ability. It is therefore unclear whether low cholesterol levels in older adults are a marker for frailty, malnutrition or subclinical disease.</p> <p>5. Research ethics- Participant consent was not noted. It does not say who filled out the questionnaire, patient or staff.</p> <p>8. References; One quite old reference was used, Lee IM et al 1996</p> <p>9. Results; the objective of evaluating prevalence of undernutrition was limited by the above, point 3</p> <p>11. Conclusion; limited by the above</p> <p>The conclusion could also have pointed out the weight range of other in-patient cohorts to elucidate what contribution to low weight could be due to diagnosis or the hospital environment.</p> <p>Known contributors to nutritional risk are food provision and intake, mealtime experience such as social eating, co-morbid psychiatric conditions such as depression or physical conditions such as frailty, swallowing difficulties, and dentition and are all worthy of exploring further.</p> <p>Page 9 , line10, relevant literature and guidelines- what are these?</p> <p>Page 12, line 12 stats for inpts v outpts given wrong way round?</p> <p>Page 15, line 4 , give the reference for study quoted</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer #1

- 1) Please report response rates both among institutions and within institutions (in the Study participants section of the Methods section as well as in Figure 1).

Response: Thank you for your suggestion. As noted above, we mailed the questionnaire to the facilities that consented to participate in the investigation. However, we were not able to obtain information from all facilities about the number of patients who refused to participate in the investigation, and could not report the overall response rate. We have added this explanation to our discussion of limitations (P21, L3–L7), and have made appropriate modifications to Figure 1.

- 2) Please report separately Overweight and Obesity (in both Figure 1 and Table 3), in order to make it possible to compare with other studies on overweight and obesity among schizophrenia patients.

Response: Thank you for this suggestion. As recommended, we have revised Figure 1 and Table 3 to separately report overweight and obesity.

- 3) Give the literature reference for the values employed to calculate the chlorpromazine equivalents (Methods section).

Response: As suggested, we have included reference to the relevant literature in our discussion of chlorpromazine equivalents (reference 14: Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry*. 2003; 64(6): 663–67.) (P9, L12–13).

- 4) Please give account of the prevalence rates of current daily smoking, hypertension and diabetes mellitus in the Japanese general population, in order to be able to compare them with data of Tables 1 and 3.

Response: As suggested, we have included information about the prevalence rates of smoking, hypertension, and diabetes mellitus in the general Japanese population, and a corresponding reference (17) in the Results section (P11, L10–11).

- 5) Please analyze the possible association of daily smoking with BMI and type and dose of antipsychotic medication.

Response: Thank you for this interesting suggestion. We performed a multivariate logistic regression analysis to assess the influence of daily smoking on BMI and type and dose of antipsychotic medication. However, daily smoking had no significant effect on BMI or type and dose of antipsychotic medication. We have added this information to method and result section. (P10, L8–10; P11, L11–13)

- 6) Please comment, in the Discussion section, on the lower rates of hypertension and diabetes mellitus among inpatients and their potential health advantage, in contrast with the disadvantage attributed to underweight among these individuals.

Response: The authors agree that this comment is particularly important. Therefore, we have included a brief discussion about this in the Discussion section (P20, L3–9).

Reviewer #2

- 1) While there is no universally accepted definition for undernutrition, the biochemical parameters given in this study are not the indicators for under nutrition typically used in clinical practice; at least

one indicator of protein status is invariably included, and also micronutrients such as iron. Note the paper Suzuki et al included hypoproteinemia. If this study had access to only those biochemical parameters given, and perhaps taken from an existing data set, that should have been made clear as a study limitation and highlighted as a point for further investigation.

Response: Thank you for highlighting this. Unfortunately, we did not have access to other biochemical parameters such as protein and iron that could indicate under-nutrition. We also recognize that there is no universally accepted definition for under-nutrition. However, a previous study reported that protein intake is associated with an increased body weight (Ankarfeldt et al. 2014, *Obesity*). Therefore, it was supposed that blood protein density correlates with body weight. Although there are various opinions of how under-nutrition is defined, there are reports that underweight relates to the risk of death. Moreover, it is easy to measure body weight in comparison with total protein, and this is easy to use in clinical practice. Therefore, we regarded body weight as one of the most important risk factors of under-nutrition. We have added a brief explanation about this in our discussion of the limitations of our study (P21, L7–L13).

2) Blood cholesterol levels – it's helpful to state that these tend to decrease with increasing age (the inpatients were significantly older than outpatients) and while low cholesterol levels are associated with increased mortality, some studies have identified that low cholesterol is associated with other markers of decreased health, including weight loss, low serum albumin, reduced functional ability. It is therefore unclear whether low cholesterol levels in older adults are a marker for frailty, malnutrition or subclinical disease.

Response: In the present study, cholesterol levels decreased with ageing. However, we could not clearly determine whether low cholesterol levels in older adults were a marker for frailty, malnutrition, or subclinical disease. As noted, the decrease in cholesterol levels in older adults is attributed to several causes. We have included a brief discussion of this in the Discussion section (P19, L14– P20, L3).

3) Research ethics - Participant consent was not noted. It does not say who filled out the questionnaire, patient or staff.

Response: Participants gave verbal consent to participate, and the questionnaire stated that returning a completed questionnaire would be taken as providing consent. Participants completed the questionnaires themselves. As suggested, we have included this information in the Methods section (P8, L15–P9, L2).

4) References; One quite old reference was used, Lee IM et al 1996.

Response: We agree with this comment and have replaced the old reference (Lee et al 1996) with a more recent reference (reference No 10): Wirth R, Streicher M, Smoliner C, et al. The impact of weight loss and low BMI on mortality of nursing home residents - Results from the nutritionDay in nursing homes. *Clin Nutr* 2015 Jun 19. pii: S0261-5614(15)00172-7. doi: 10.1016/j.clnu.2015.06.003 [Epub ahead of print].

5) Results; the objective of evaluating prevalence of undernutrition was limited by the above point (study design).

Response: As noted, we did not have other biochemical parameters that could indicate the under-nutrition status. Please see our response to this comment above, and our discussion of this in the limitations section (P21, L7–13).

6) Conclusion; limited by the above The conclusion could also have pointed out the weight range of other in-patient cohorts to elucidate what contribution to low weight could be due to diagnosis or the hospital environment. Known contributors to nutritional risk are food provision and intake, mealtime experience such as social eating, co-morbid psychiatric conditions such as depression or physical conditions such as frailty, swallowing difficulties, and dentition and are all worthy of exploring further.

Response: Thank you for your helpful comments. We agree with the points that have been highlighted. We have not discussed underweight in relation to other mental diseases; however, if underweight is a problem peculiar to patients with schizophrenia, it may be necessary to include appropriate nourishment instruction in the management of patients with schizophrenia. We would like to refer to these comments in a future study.

7) Page 9, line10, relevant literature and guidelines- what are these?

Response: We investigated the health consciousness of the participants, but did not discuss this examination in the present study. Therefore, we deleted this sentence.

8) Page 12, line 12 stats for inpts v outpts given wrong way round?

Response: Thank you for pointing this out. We have made the appropriate revision (P15, L4–5).

9) Page 15, line 4, give the reference for study quoted

Response: Thank you for noting this. We have m

VERSION 2 – REVIEW

REVIEWER	manuel Gurpegui, M.D. Department of Psychiatry, University of Granada, Granada, Spain
REVIEW RETURNED	05-Oct-2015

GENERAL COMMENTS	The authors have addressed appropriately the issues pointed by both reviewers and the paper is now ready for publication. However, three minor points would result in further improvement: 1) Some results given provide in Table 1 should be commented, in the Discussion section, in their contrast with the general population data: smoking, 36.2% in outpatients and 24.0% in inpatients (vs. 20.1% in the Japanese general population); hypertension, 30.5% and 19.9% (vs. 27.2%); and diabetes mellitus, 16.8% and 7.1% (vs. 10.9%) respectively. 2) Please indicate the percentages in each BMI category in the first two lines of Table 3 and comment about their contrast with both the Japanese general population and with previous studies in Japanese (e.g., reference 11) or in Western clinical samples (e.g., reference 4). 3) In order to avoid inappropriate causal inferences, the authors should not use the expression “the effect of daily smoking on BMI and type and dose of antipsychotic medication” but rather “the association of ...” in the Methods (page 10) and the Results section (page 11 of the revised manuscript).
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REVIEWER	Arleen Rowell St Andrews Healthcare, Northampton, England, UK
REVIEW RETURNED	08-Oct-2015

GENERAL COMMENTS	<p>Thank you for addressing the previous review comments. A minor point but some phrases below appear to be directly from my review comments, therefore to avoid any concerns re plagiarism please reword.</p> <p>Page 19 of 66</p> <p>We could not clearly determine whether low cholesterol levels in older adults were a marker for frailty, under-nutrition or subclinical disease. It may be that there are various causes involved with low cholesterol levels in older adults, such as weight loss, low serum albumin, and reduced functional ability.</p> <p>With very best wishes for this publication and your on-going work.</p>
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VERSION 2 – AUTHOR RESPONSE

To Reviewer 1

Response 1): Thank you for your suggestion. As you suggested, We have added comments to discussion section (P23 L4–9). However, I did not add comments about HT and DM, because I described it on the same paragraph (P22 L14- P23L4).

Response 2): Thank you for this suggestion. As you suggested, we have revised Table 3, and added comments to discussion section (P20 L2–8).

Response 3): As you pointed out, we revised the manuscript (P10L9, P11L12).

To Reviewer 2

Response): As you suggested, we revised the manuscript (P22L11-14).