Efficacy of nanocurcumin supplementation on insulin resistance, lipids, inflammatory factors and nesfatin among obese patients with non-alcoholic fatty liver disease (NAFLD): a trial protocol

Seyed Ali Jazayeri-Tehrani,¹ Seyed Mahdi Rezayat,²,3,4 Siavash Mansouri,⁵ Mostafa Qorbani,⁶ Seyed Moayyed Alaviani,⁷ Milad Daneshi-Maskooni,⁸ Mohammad-Javad Hosseinzadeh-Attar¹

ABSTRACT

Objectives  Different studies have been conducted on the role of curcumin in health since having multiple properties, including antioxidant and anti-inflammatory effects. Due to the lack of studies regarding curcumin effects on obese patients with non-alcoholic fatty liver disease (NAFLD), our protocol was designed to assess nanocurcumin impacts on blood sugar, lipids, inflammatory indices, insulin resistance and liver function, especially by nesfatin.

Setting  This trial will be conducted in the Oil Company central hospital of Tehran, Iran with a primary level of care.

Participants  84 obese patients with NAFLD diagnosed using ultrasonography will be employed according to the eligibility criteria.

Interventions  The patients will be randomly divided into two equal groups (nanocurcumin and placebo, two 40 mg capsules per day with meals for 3 months, follow-up monthly). Also, lifestyle changes (low-calorie diet and physical activity) will be advised.

Measures of the primary and secondary outcomes  A general questionnaire, 24 hours food recall (at the beginning, middle and end) and short-form International Physical Activity Questionnaire will be completed. Blood pressure, anthropometrics, serum sugar indices (fasting blood sugar and insulin, insulin resistance and sensitivity and glycosylated haemoglobin), lipids (triglyceride, total cholesterol and low-density and high-density lipoprotein-cholesterol), inflammatory profiles (interleukin-6, high-sensitivity C-reactive protein, and tumour necrosis factor-alpha), liver function (alanine and aspartate transaminase) and nesfatin will be measured at the beginning and end of the study.

Conclusion  This trial would be the first experiment to determine nanocurcumin efficacy on certain blood factors among obese patients with NAFLD. Nevertheless, studying the potential consequences of curcumin in various diseases, especially NAFLD, is required for clinical use.

Trial registration number  IRCT2016071915536N3; pre-results.

Strengths and limitations of this study

► Providing a randomised double-blinded design and protocol publication.
► Determining dietary intake and physical activity statuses and registering any possible patient-reported problems.
► Selecting a single and slow polyclinic recruitment of the patients to satisfy the eligibility criteria.
► Self-reporting of the dietary intake and physical activity statuses and lack of cooperation of some participants to complete the intervention.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) occurs when triglyceride (TG) is deposited in liver cells. Intrahepatic TG (IHTG) content of more than 5% of liver weight or volume or visible intracellular TG content of 5% of hepatocytes or more are chemically or histologically defined as excessive IHTG or steatosis, respectively.¹ The three degrees of NAFLD are mild (<33% of fat accumulation), moderate (33%–66% of fat accumulation) and severe (>66% of fat accumulation).²

The standard method of diagnosis is liver biopsy. Since biopsy is an invasive method, non-invasive diagnostic approaches, such as ultrasound examination, CT scan and MRI, are mostly employed. However, it is difficult to exactly differentiate between the disease stages by these techniques. Most patients with NAFLD are implicitly identified via elevated liver enzymes (aminotransferases: alanine transaminase (ALT) and aspartate transaminase (AST) contents of about 1.5–2 times higher than normal levels) in
medical examinations. According to the recent studies, many patients with advanced non-alcoholic steatohepatitis (NASH) and even cirrhosis can have normal levels of liver enzymes.\textsuperscript{3,4} Thus, NAFLD prevalence is probably more than what has been reported. Its symptoms often include fatigue and discomfort in the right upper quarter of the abdomen. Its average prevalence in adults is about 30\% (nearly 65\%–85\% and 15\%–20\%) in obese (body mass index (BMI) ≥25) and non-obese (BMI <25) patients, respectively.\textsuperscript{7–11} NAFLD is more common in men. The disease pathology is a two-phase event, including fat reposition in hepatocytes following hepatic steatosis and NASH. Insulin resistance has a key role in both phases, while oxidative stress and pro-inflammatory cytokines are the major irritants.\textsuperscript{12} The common causes of macrovascular steatosis include insulin resistance, increasing blood insulin levels, central obesity, diabetes type 2, medications (eg, glucocorticoid, oestrogen, tamoxifen and amiodarone), nutrition status (starvation, protein deficiency and choline deficiency), liver diseases (Wilson’s disease and chronic hepatitis C-III), Hindi child cirrhosis and jejenum bypass.\textsuperscript{6} Liver fat content is directly related to insulin resistance. Activation of nuclear factor kappa-light-chain-enhancer of activated B cells upregulates the production of pro-inflammatory cytokines that influence the insulin activity. Thus, inflammation, adipokines, oxidative stress or lipid metabolites can change insulin sensitivity, but intrahepatic fat content is not necessarily directly related to any of them.\textsuperscript{1} Age, family history, malnutrition, severe weight loss, gastrointestinal tract infection, certain medication and some diseases, such as inflammatory bowel disease are the other risk factors of NAFLD.\textsuperscript{14–15} In some studies, the disease incidence has been related to the high intakes of saturated fats or carbohydrates.\textsuperscript{16,17} Some patients have normal weights although they may have abdominal obesity and insulin resistance.\textsuperscript{18,19}

Nesfatin as a neuropeptide secreted by the hypothalamus in mammals is involved in the regulation of appetite and body fat stores. Nesfatin gene is expressed in other locations, such as brain, pancreas, endocrine cells of stomach and adipocytes. Nesfatin gene expression is activated by peroxisome proliferator-activated receptors (PPARs), especially PPAR\textsubscript{γ}. Nesfatin plays an important role in glucose metabolism, phosphorylation of certain signalling proteins and increasing insulin sensitivity in the liver, particularly through AMP-activated protein kinase.\textsuperscript{20,21} In a recent study, the serum levels of nesfatin in overweight/obese patients with NAFLD with an age of 30–60 years were found to be significantly lower than those of the healthy group.\textsuperscript{21}

A common treatment for NAFLD is changing the lifestyle (gradual weight loss and increasing physical activity) that can improve liver enzymes, fat reposition, inflammation and fibrosis.\textsuperscript{22–27} It seems that changes in the dietary ingredients can be presented as a therapy method for these patients\textsuperscript{28,29} since losing weight and its maintenance for a long period of time is a hard task.\textsuperscript{30} Accordingly, assessment of the relationship between NAFLD and certain nutrients or dietary ingredients is very important.

Different studies have been conducted on the roles of curcumin in health. Curcumin as a turmeric spice of the ginger family has multiple properties, including antioxidant, anti-inflammatory, antimicrobial and anti-carcinogenic effects.\textsuperscript{31–38} Due to the importance of PPARs in the metabolic pathways, numerous studies have been carried out to investigate curcumin effects on PPARs, especially on PPAR\textsubscript{γ} gene expression. It increases both the activity and expression of PPAR\textsubscript{γ}, which is important for inhibiting inflammation and oxidative stress as the main factors of insulin resistance and NAFLD.\textsuperscript{39–42}

NAFLD prevalence and implications are increasing. Due to the lack of any drugs for it and the role of nutrition (weight loss and changing food components associated with increased physical activity) as the key factor of treatment, assessment of the effects of some food components like curcumin as a polyphenol on NAFLD improvement can further help to find new ways of treatment. Curcumin plays numerous metabolic roles in the improvement of insulin resistance through its antioxidant, anti-inflammatory, hypolipidaemic and antimicrobial effects. Despite the multiple benefits of curcumin for health, it has a very low stability and bioavailability that affect its efficacy in therapy. Recently, many approaches have been assessed to improve its stability and bioavailability by using polymeric nanoparticles named nanocurcumin. For example, poly(lactic-co-glycolic acid (PLGA) nanoparticles can increase curcumin bioavailability up to 22 times.\textsuperscript{43} Hence, in this study, nanocurcumin was applied. Fat accumulation in the liver, inflammation and oxidative stress result in NAFLD onset and progression, which may be improved by curcumin. NAFLD exacerbates with overweight or obesity; yet, no human studies have been conducted on curcumin effects on them. Thus, this study aimed to assess the effects of curcumin on blood glucose, lipid, inflammatory profiles, liver function (fatty liver degree, ALT and AST) and insulin resistance (homeostasis model assessment-insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI), especially through nesfatin in obese patients with NAFLD.

METHODS

Study design

In this research, a double-blind randomised clinical trial will be performed.

Objectives

1. Comparing the subjects’ economic, occupational and marital statuses, as well as education levels with nanocurcumin and placebo supplantations before the intervention
2. Comparing the means of serum TG, low-density lipoprotein cholesterol, total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, fasting blood sugar (FBS), insulin, haemoglobin A1c (HbA1c), insulin resistance, sensitivity indices (HOMA-IR, QUICKI), tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP) and nesfatin within each group and between the two groups before and after the intervention
3. Comparing the means of weight, waist circumference, BMI, body composition percentage and systolic and diastolic blood pressures within each group and between the two groups before and after the intervention
4. Comparing the means of physical activity score and energy intakes, micronutrients and macronutrients within each group and between the two groups before and after the intervention
5. Comparing the means of age and height between the two groups before the intervention

**Inclusion criteria**
1. Age: 25–50 years.
2. Overweight/obesity (25 ≤BMI<35).
3. NAFLD diagnosis by a radiologist based on the ultrasound test.
4. An informed consent.

**Exclusion criteria**
1. A history of alcohol consumption during the last 12 months based on personal admission.
2. Regular intakes of non-steroidal anti-inflammatory drugs, antibiotics and corticosteroids during the last 6 months.
3. Misuses of narcotics, psychotropic medication and cigarettes over the last 6 months.
4. Intakes of antisecretory drugs causing achlorhydria, amiodarone, valproate, prednisone, tamoxifen, perhexiline and methotrexate, liver fat-inducing drugs, hormone drugs, statins, antihypertensives and ursodeoxycholic acid during the last 6 months.
5. Intakes of supplements, such as probiotics, multivitamins/minerals, antioxidants and omega-3 at least twice a week during the study or the last 3 months.
6. Diagnosis of pathological conditions affecting the liver, such as viral hepatitis, acute or chronic liver failure, cholestasis, liver transplantation, acute systemic disease, cystic fibrosis disease, muscular dystrophy, previous gastrointestinal surgery, neurological disorders, structural abnormalities of the gastrointestinal tract, diabetes, heart failure, thyroid disorders, kidney diseases, respiratory failure, psychological disorders, hereditary haemochromatosis, Wilson’s disease, alpha-1 antitrypsin deficiency, autoimmune diseases, coeliac disease and any types of malignancy.
7. Rapid weight loss, total parenteral nutrition and protein malnutrition over the last 6 months.
8. NAFLD secondary causes, such as drugs, surgical procedures and environmental toxins.
9. Conditions leading to physical disability.
10. Uncontrolled hypertension (>140/90 mm Hg).
11. Breast feeding, pregnancy or a plan for pregnancy in the next 3 months.
12. Being a professional athlete or doing regular exercise.
13. Taking no more than 10% of the prescription supplements.

**Subjects**
The patients will be referred to a major executor after being diagnosed by a radiologist if meeting the eligibility criteria at the central hospital of the polyclinic of the National Iranian Oil Company (NIOC), Tehran, Iran. At the beginning, all the study details will be clarified and an informed consent form will be provided. Then, a general questionnaire, the short form of International Physical Activity Questionnaire (IPAQ), and 24 hours food recall questionnaire will be filled out by the interviewer. The necessary lifestyle changes, including a low-calorie diet (weight loss of 0.5–1 kg per week based on BMI during the trial) and increased physical activity (aerobic exercise of moderate intensity about 30–45 min at least three times a week) will be prescribed. Anthropometrics, including weight, height and waist circumference will be measured using a digital scale, stadiometer and non-elastic tape, respectively. Weight without shoes and minimum clothing looking frontwards with an accuracy of 0.5 cm and waist circumference in the middle of the last rib and the iliac crest with minimal clothing with an accuracy of 0.5 cm will be measured.

The questionnaire of 24 hours food recall will be completed at the beginning, middle and end of the study. Blood pressure will be measured with a manometer (cuff in two-thirds of the upper right arm) after 10 min of resting in a sitting position at the beginning and end of the study. At both the beginning and end of the intervention, 10 mL of blood will be taken from the brachial vein to measure the mentioned factors. Finally, these measurements will be privately presented to the patients.

**Sample size**
According to Chuangsamarn et al.14, the mean±SD of HOMA-IR index in the curcumin and placebo groups were 3.22±1.30 and 4.08±1.35, respectively. The sample size was 42 patients in each group with a CI of 95%, power of 80% and loss of 15%. A total of 84 patients will be invited and divided into two equal groups by using the block randomisation method as follows:
1. 42 overweight/obese patients with NAFLD with nanocurcumin supplement and advice on lifestyle changes (a weight loss diet and increase of physical activity) for 3 months of intervention.

2. 42 overweight/obese patients with NAFLD with the placebo supplement and advice on lifestyle changes (a weight loss diet and increase of physical activity) for 3 months of intervention.

**Intervention and randomisation**

The block randomisation method was used to divide the patients into two equal groups. Age and gender distributions will be controlled using a stratified randomisation. The supplementation ratio is 1:1 for the groups in this study. An assistant performed the block randomisation and the intervention allotment will be blinded to the investigator and patients. The subjects will be randomly allocated into the two groups of taking nanocurcumin and placebo supplements. The supplements offered in A and B packages will be blinded to the investigators and participants.

No side effects and toxicity caused by taking 210 mg of nanocurcumin have been reported. The supplementation dose of Sinacurcumin is 80 mg/day (two 40 mg capsules per day according to company’s order: one capsule with breakfast and one with dinner). Sinacurcumin and placebo supplements will be prepared by Exir-nanosina Pharmaceutical Company. The placebo supplement contained polysorbate 80, soy oil, purified water, sorbitol 70, methyl paraben and propyl paraben associated with nanocurcumin particles.

Curcumin is of a very low stability and bioavailability. It is hardly dissolved in water, rapidly metabolised and very weakly absorbed in the intestine so that it remains at a very low level in plasma. Human studies have shown that a daily consumption of 12 g of curcumin is safe. Less than 1% of curcumin taken enters the bloodstream to be mostly metabolised in the liver. Today, new ways are being investigated to enhance curcumin bioavailability, especially through polymeric nanoparticles called nanocurcumin. PLGA as a nanoparticle can augment curcumin bioavailability in mice up to 22 times.

The supplements will be distributed on a monthly basis, while any possible complications regarding the numbers of ingested capsules and packets given back will be recorded. Also, the study progress will be pursued by calling the subjects once a week.

**Lifestyle changes**

A low-calorie diet for a weight loss of 0.5–1 kg/week based on the BMI and increased physical activity will be presented as the lifestyle changes by a qualified dietitian present in the central hospital of the polyclinic of NIOC, Tehran, Iran.

**Assessments and measurements**

The ultrasound test will be done by a radiologist after 12 hours of fasting. The measurements of blood lipids (TC, HDL, LDL and TG) and liver enzymes (ALT and AST) will be determined using special kits and Hitachi analyser (or BT-3500) device after 12 hours of fasting. Blood sugar (FBS) is determined using the glucose oxidase method. Fasting blood insulin (FBI) and HbA1c will be measured via electrochemiluminescence application using cobas e411 analyser device and immunoturbidimetric method. Insulin resistance and sensitivity indices (HOMA and QUICKI) are calculated according to the following formula:

\[
\text{QUICKI} = \frac{1}{\log (\text{FBI } \mu U/mL)} + \log (\text{FBS } \text{mg/dL})
\]

\[
\text{HOMA} = \frac{(\text{FBI } \mu U/mL) \times \text{FBS } (\text{mmol/l})}{22.5}
\]

The serum inflammatory markers (IL-6, TNF-α and hs-CRP) and nesfatin will be determined using the ELISA method (sandwich ELISA format) and specific kits. The ELISA test will be done using Elisa washer (Combivash Human) and bioElisa reader devices (biokit EL, 800).

Food intake status at the beginning, middle and end of the study and physical activity at the beginning and end of the study will be investigated using the questionnaire of 24 hours food recall and the short form of IPAQ. The dietary intakes will thus be examined and controlled. The body composition percentage, including body fat and lean body mass will be determined using Bioimpedance Analyzer device (Tanita).

At the beginning and end of the study, the systolic and diastolic blood pressures will be determined using a mercury manometer. The values are reported in mm Hg. Waist circumference, weight and height will be measured using a non-elastic tape, digital scale and stadiometer, respectively. Weight with minimal clothing without shoes (100 g accuracy), height in a standing position without shoes with heels sticking to the wall and head keeping flat and looking forward (0.5 cm accuracy) and waist circumference at the middle of the last rib and the iliac crest with minimal clothing were measured at the beginning and end of the study. Blood taking, storage of blood samples and performance of the laboratory tests will be conducted at the central hospital of the NIOC, Tehran, Iran.

The details of enrolments, interventions and assessments are presented in table 1. Furthermore, the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist was completed in an additional file. The trial progress will be regularly and independently checked by an assistant.

**Data analysis**

The data entry, coding, security and saving will be checked. The data normality will be examined using a Kolmogorov-Smirnov test. Non-parametric/\(\chi^2\), Wilcoxon, analysis of covariance and Pearson’s correlation coefficient statistical tests as well as t-test will be applied. A CI of 95% will be considered in all the tests. The significance value is considered to be less than 0.05. Finally, SPSS16 statistical software will be applied to analyse the data.
Table 1 Contents of enrolments, interventions and assessments.

<table>
<thead>
<tr>
<th>Trial contents</th>
<th>Study period</th>
<th>Enrolment</th>
<th>Allocation</th>
<th>Postallocation</th>
<th>Close-out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timepoint</td>
<td>-t&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0</td>
<td>+1 Month</td>
<td>+1.5 Months</td>
<td>+2 Months</td>
</tr>
<tr>
<td>Enrolments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligibility screen</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General questionnaire</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hours food recall</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>SF-IPAQ questionnaire</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Anthropometrics</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other questionnaires</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood taking</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allocation</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Intervention A)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>(Intervention B)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Assessments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dietary status</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory factors</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid profile</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sugar indices</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nesfatin</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity status</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthropometrics</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SF-IPAQ, Short-Form International Physical Activity Questionnaire.

**Data accessibility**

Accessibility to the ultimate data set is only limited to the major investigator. The results will be presented only via publication.

**DISCUSSION**

This is a novel study proposed for the first time with regard to the evaluation of nanocurcumin efficacy on various parameters, such as blood sugar, lipids, inflammatory markers, insulin resistance and nesfatin among overweight/obese patients with NAFLD. It is of high relevance due to the various clinical uses of curcumin and lack of any studies related to its advantages or disadvantages in patients with NAFLD. However, curcumin clinical practice for the treatment of some disorders needs to be investigated, while taking into account its possible prospective applications for several diseases, especially NAFLD. Due to the increasing values of obesity and NAFLD associated with significant alterations of some blood factors and the presence of few studies on nanocurcumin efficacy, the proposed research aimed to select these groups of patients as the most pertinent participants for intervention.

The strengths of the trial are using a randomised double-blind design and protocol publication, determining dietary and physical activity statuses and registering any possible patient-reported problems.

The trial limitations are patients’ slow recruitments and increase of the study period due to the multiple eligibility criteria, selection of a single polyclinic centre, participants’ self-reporting on the drugs and supplement consumptions, dietary intakes and physical activities and lack of cooperation of some participants to complete the intervention, which would lead to a replacement with other patients if the loss percentage will be more than expected.

**Trial status**

The patients’ employments were continued at the time of the protocol submission.

**Author affiliations**

1Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, International Campus, Tehran University of Medical Sciences (IC-TUMS), Tehran, Iran
Acknowledgements The support of Tehran University of Medical Sciences and cooperation of the central hospital of the NIOC, Tehran, Iran, are acknowledged. 

Contributors SAJT, MJHA and SMR conceived and developed the idea for the study and revised the manuscript. SM, SMA and MDM contributed to data collection. MDM wrote numerous drafts of the study. M0 contributed to statistical interpretations. All authors read and approved the final manuscript.

Funding The trial funding was supported by Tehran University of Medical Sciences.

Competing interests None declared.

Patient consent Detail has been removed from this case description/ these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Ethics approval The ethical approval of this trial was conducted by the ethics committee of Tehran University of Medical Sciences (Ethical Code: IR.TUMS.REC.1395.2612). All the participants will complete an informed consent form (in Persian). Participation in and continuation of the supplementation is free and voluntary for the patients. In the trial, advice on the lifestyle modification will be presented to the patients free of charge. The health care services of the hospital will be provided without inconsistency. The side effects of the supplements had not been previously published. The patients’ personal information will be kept confidential.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement There are no additional data to share.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is expressly granted.

REFERENCES


Efficacy of nanocurcumin supplementation on insulin resistance, lipids, inflammatory factors and nesfatin among obese patients with non-alcoholic fatty liver disease (NAFLD): a trial protocol

Seyed Ali Jazayeri-Tehrani, Seyed Mahdi Rezayat, Siavash Mansouri, Mostafa Qorbani, Seyed Moayed Alavian, Milad Daneshi-Maskooni and Mohammad-Javad Hosseinzadeh-Attar

BMJ Open 2017 7:
doi: 10.1136/bmjopen-2017-016914

Updated information and services can be found at:
http://bmjopen.bmj.com/content/7/7/e016914

These include:

References
This article cites 41 articles, 3 of which you can access for free at:
http://bmjopen.bmj.com/content/7/7/e016914#BIBL

Open Access
This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Nutrition and metabolism (322)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/