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# Effects of tocotrienol-enriched oat supplementation on metabolic profile, nutritional status and health-related quality of life among patients with metabolic syndrome†

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**Background:** Tocotrienol has garnered significant attention due to its potent antioxidant and anti-inflammatory effects in ameliorating cardiovascular-related comorbidities. The present study aimed to elucidate the effects of tocotrienol-enriched oat supplementation on individuals with metabolic syndrome (MetS). **Method:** This was a randomized, double-blind, placebo-controlled human clinical trial. Patients with MetS were randomized to the tocotrienol-enriched oat (TO), oat (O) or control (C) groups. Both TO and O groups were supplemented twice daily for 12 weeks, while group C did not receive any intervention. Changes in the metabolic profile of individuals were considered as the primary endpoint. The secondary endpoints included the morphological assessment of nutritional and anthropometric parameters and health-related quality of life. Other measurements included compliance and tolerability to the study regime. **Results:** The rate of MetS remission in the TO and O groups was approximately twice than that in the control group (37.0% vs. 18.5%). After 12 weeks, the TO group showed significant improvements in the fasting blood glucose (−4.5%), blood pressure (systolic: −4.2%; diastolic: −5.3%), high density lipoprotein-cholesterol (HDL-C) (+34.1%), and triglyceride (−7.1%) ( $p < 0.05$ ) levels. Group TO demonstrated an increase in muscle mass (+0.301 kg,  $p < 0.05$ ) and reduced body fat (−0.775%,  $p < 0.05$ ). Both the TO and O groups showed improvements in the overall HR-QoL, and the visual analogue scale (VAS) score. **Conclusion:** Twelve weeks of tocotrienol-enriched oat supplementation improved surrogate endpoints associated with MetS. This complementary dietary management approach may be more effective at alleviating MetS symptoms than the pharmacological approach alone and could be a safe dietary strategy for secondary prevention.

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## Introduction

Metabolic syndrome (MetS) is a clinical cluster of metabolic and vascular disorders that are often accompanied by obesity and overweight.<sup>1</sup> Although there is no unified declaration on the diagnostic criteria, experts agree that this syndrome is characterized by impaired insulin sensitivity, hyperglycemia, dyslipidemia, abdominal obesity and hypertension.<sup>1</sup> MetS increases the risk of cardiovascular events, stroke, type 2 diabetes mellitus (T2DM), and all-cause mortality.<sup>2</sup> As the prevalence of MetS has reached epidemic levels across the globe, individuals with specific conditions are confronted with a sub-

stantially increased risk of developing severe complications. As such, an immediate and all-encompassing approach for detecting, preventing, and managing MetS is crucial for alleviating its impact on public health. The economic burden associated with managing MetS-related complications is substantial, underscoring the importance of early intervention and effective treatment strategies.<sup>2</sup>

Evidence on the effectiveness of dietary control on metabolic parameters has been established, emphasizing its promising therapeutic effects in combination with pharmaceutical therapy.<sup>3</sup> Among the currently implemented dietary interventions, increased consumption of whole grains and, in particular, oat components, such as oat fibre and oat bioactive constituents, has been strongly suggested to regulate metabolic indicators, including blood cholesterol, blood glucose, body mass index (BMI), and lipid profiles.<sup>4</sup> These dietary modifications are associated with a reduced risk of cardiovascular disease.<sup>5,6</sup>

In 1997, the Food and Drug Administration (FDA) acknowledged the beneficial role of fibre in reducing cardiovascular

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disease risk.<sup>7</sup> Products with 0.75 g of  $\beta$ -glucan or 1.78 g of psyllium for each serving are qualified to carry the health claim of “will reduce the risk of coronary heart disease” and further suggest that 4 servings of these foods are effective daily dosages.<sup>8</sup> More recently, the European Food Safety Authority,<sup>9</sup> the French Agency for Food, Environment and Occupational Health and Safety,<sup>10</sup> the Joint Health Claims Initiative in the UK and the Food Directorate,<sup>11</sup> and the Health Products and Food Branch of Health Canada<sup>12</sup> have made claims for cholesterol-lowering effects at this level of  $\beta$ -glucan intake.

The metabolic regulatory effects of oats are attributable to their high contents of antioxidants, phenolic compounds, and  $\beta$ -glucan. While whole-grain oats reduced low density lipoprotein-cholesterol (LDL-C) and total cholesterol (TC) with no apparent effects on high density lipoprotein-cholesterol (HDL-C),<sup>13</sup> oat-derived  $\beta$ -glucan has been shown to increase HDL-C and improve LDL-C among overweight individuals.<sup>14</sup> Daily consumption of at least 3 g of oat  $\beta$ -glucan per day reduced TC and LDL in normo- and hypercholesterolaemic individuals.<sup>15</sup> The mechanism by which oat  $\beta$ -glucan mediates cholesterol-lowering effects is through the action of forming a viscous layer in the small intestine, thereby inhibiting the intestinal uptake of dietary cholesterol and reabsorption of bile acids.<sup>15</sup> The inhibition of bile reabsorption therefore enhances the synthesis of bile acids from cholesterol and minimizes the circulating LDL-C level.<sup>16</sup> Oat-based interventions enriched with  $\beta$ -glucan, such as those reported by Saltzman *et al.* (2001) and Maki *et al.* (2010), were effective in reducing systolic blood pressure (SBP) and waist circumference (WC), respectively, in parallel to the significant body fat reduction.<sup>17,18</sup> In overweight individuals, Beck *et al.* (2010) observed reductions in HDL-C, body weight and WC with higher  $\beta$ -glucan intake,<sup>19</sup> while Charlton *et al.* (2012) reported decreased SBP, body fat and body weight in hypercholesterolemic patients.<sup>20</sup> In addition, longitudinal studies have demonstrated the significant improvements in triglycerides (TG), fasting blood glucose (FBG), body weight, and WC in MetS patients,<sup>21,22</sup> highlighting the benefits of prolonged oat intake.

In another arm, tocotrienol has emerged as a trending subject of scientific scrutiny, captivating researchers because of its remarkable antioxidant properties that surpass those of tocopherol. Tocotrienols differ from tocopherols in the presence of three unsaturated bonds. Human research using clinical trial approaches indicated an improvement in HDL-C levels with the provision of tocotrienol but not with TC, LDL-C or triglyceride (TG) markers.<sup>23</sup> The therapeutic outcome of tocotrienol has been established; however, the extent to which the therapeutic effects are commendable is still unclear. Tocotrienol, an isolated compound, has been proven to be effective in regulating MetS risk factors,<sup>23</sup> but its synergistic effect with oats has yet to be elucidated. Tocotrienol-based interventions, such as those conducted by Magosso *et al.* (2013) and Heng *et al.* (2015), led to reductions in TG and diastolic blood pressure (DBP) and increased HDL-C, though body composition changes were minimal.<sup>24,25</sup> In non-alcoholic fatty liver disease (NAFLD) patients, Pervez *et al.* (2018) reported

improvements in TG, WC, and body mass index (BMI) with  $\delta$ -tocotrienol supplementation,<sup>26</sup> while Fatima *et al.* (2023) found reductions in BP, TG, and FBG alongside increased HDL-C.<sup>27</sup> These findings emphasized the individual potential of oat and tocotrienol interventions, respectively, for managing MetS.

Mounting evidence has demonstrated significant correlation between MetS and worsening quality of life (QoL).<sup>28–30</sup> Typically, persistent MetS results in a decline in the mental domain; however, this could be reversed through the remission of MetS.<sup>31</sup> Further scrutinization of MetS components revealed that hypertriglyceridemia and abdominal obesity were associated with increased odds of having poor QoL.<sup>29</sup> Given that MetS has been closely linked to poor QoL, it is crucial to explore its impact on alterations in self-perception of well-being.<sup>32,33</sup> The effects of MetS on QoL have not been clearly established, but the effects of MetS on obesity, diabetes and hypertension are evident.

To the best of our knowledge, this is the first human clinical trial aimed at evaluating the effects of tocotrienol-enriched oats as a functional food in patients with MetS. Our primary endpoint included the changes in metabolic parameters at the baseline and after the intervention, while the secondary endpoint evaluated the changes in the nutritional status and health-related QoL, as well as compliance and tolerability towards the study regime. The compliancy of the subjects to the supplement regime was determined through the sachet count. Participants were considered “non-adherent” if they failed to consume at least 80% of the prescribed intervention regime, which is the common threshold in clinical practice.

## Materials and methods

### Trial design

This was a single-centre, double-blind, placebo-controlled trial. Study recruitment and enrolment began in March 2022, and was completed in July 2022. Subjects allocated to Group TO (tocotrienol-enriched oats) or Group O (oats) were supplemented from August 2022 onwards for 12 weeks. Sociodemographic and medical background data were retrieved from the medical database. The pre-existing medical conditions of the subjects were assessed based on the medical history and report as indicated in the patient's electronic database. Face-to-face interviews were conducted to gather all other information, including lifestyle, physical activity, dietary recall and anthropometric measurements. This trial adhered to the CONSORT guidelines for reporting randomized controlled trials.

### Study population

Subjects in this clinical trial were recruited among patients referred to the Universiti Sains Malaysia Bertam Medical Centre. The inclusion criteria were those who were aged 18 years and older and met  $\geq 3$  out of 5 Third Report of the National Cholesterol Education Program III (NCEP-ATP III)<sup>1</sup>



criteria for MetS. Individuals were excluded if they had liver, kidney, or haematological disorders, had cancer or other endocrine disorders, had alcohol or drug abuse, had hormone replacement therapy, had used steroids, chemotherapy, immunosuppressants, or radiotherapy, or if they were pregnant women or lactating mothers. Subjects who were taking antioxidant or anti-inflammatory supplements were excluded from the study (examples of antioxidants: vitamin C, vitamin E, grape seed extract, garlic capsule and *Ginkgo biloba* and examples of anti-inflammatory supplements: fish oil, curcumin extract, ginger extract and *Spirulina*). All subjects continued the prescribed medication. They were reminded not to alter their lifestyle and exercise practice throughout the trial period.

### Diagnostic criteria

The identification of MetS was abided by the NCEP-ATP III criteria.<sup>1</sup> The NCEP ATP-III report proposed the use of five criteria for the diagnosis of MetS, including WC (>102 cm for males; >88 cm for females); serum TG level (>1.69 mmol L<sup>-1</sup>, or on pharmacological treatment); serum HDL-C level (<1.13 mmol L<sup>-1</sup> for males; <1.3 mmol L<sup>-1</sup> for females, or on pharmacological treatment); BP (≥130/85 mmHg, or on pharmacological treatment) and FBG level (≥5.6 mmol L<sup>-1</sup>, or on pharmacological treatment). Individuals meeting three out of these five criteria were classified as having MetS (Table 1).

### Randomisation and blinding

Randomization was conducted by a research statistician who had no direct involvement with the current study. The random allocation sequence was generated using a computer-generated list of random numbers, with allocation concealed in sealed, numbered envelopes. Simple randomization, with a 1:1:1 allocation ratio (TO:O:C), was applied.

We applied a double-blind approach treatment assignment dedicated to Group TO (treatment group) and Group O (placebo). Eight distinct blinding considerations were applied: (1) subjects, (2) care providers, (3) data collectors, (4) trial researchers, (5) laboratory technicians, (6) outcome assessors, (7) outcome adjudicators, and (8) statisticians. Treatment assignment was withheld from these groups until the completion of the trial. In order to evaluate the effects of the trial regimen, the C group (control) did not receive any trial treat-

ment, but served as a baseline for the currently used standard medical care. Hence, only 6 distinct blinding considerations (data collectors, trial researchers, laboratory technicians, outcome assessors, outcome adjudicators, and statisticians) were applied in the C group.

### Intervention, placebo and control groups

Subjects in the Group TO and Group O received identical products in terms of appearance, taste, and packaging. Subjects were assigned randomly to either one of the intervention groups, namely, the Toco Oat (Group TO, 2 sachets, each sachet containing 30 g of oats + 50 mg of tocotrienol), Oat (Group O, 2 sachets, each sachet containing 30 g of oats), or control (Group C, no intervention), for up to 12 weeks. The tocotrienol-enriched oat was sponsored by Bioley Toco Oats™. Both the TO and O groups were scheduled to the medical center to receive and replenish the functional food at the baseline, week 4 and week 8, respectively. Group C did not receive any intervention treatment. The nutritional information for both the Toco Oat and Oat groups are shown in Appendix 1. All subjects continued their prescribed medication as usual. Safety, tolerability, and compliance were assessed concurrently. Subjects were reminded not to alter their habitual dietary intake throughout the clinical trial period. All subjects were instructed to maintain their pre-existing physical activity, lifestyle and medications, if any, throughout the study (Fig. 1).

### Study visits and measurements

Five levels of study visits were used in this trial: (1) recruitment, screening, and informed consent; (2) randomization and blinding; (3) enrolment; (4) follow-up; and (5) post-intervention assessment. Fig. 2 illustrates the schematic diagram of the trial administration.

### Primary endpoint

The subjects' outcome measures were assessed at two time points: at the baseline and at the end of the intervention period (post week 12). The primary aim of this study was to determine the changes in the MetS diagnostic criteria. The evaluation of primary outcomes included changes in serum TG (mmol L<sup>-1</sup>), HDL-C (mmol L<sup>-1</sup>), FBG (mmol L<sup>-1</sup>), systolic/diastolic BP (mmHg), and WC (cm). All biochemical parameters were tested in the routine clinical laboratory in the medical centre. A biochemical analyser, the DXC AU700 Clinical Chemistry Analyser (Beckman Coulter, USA), was used to quantify all biochemical parameters. The intra-assay coefficients of variation (CVs) for uric acid, triglycerides, total protein, and glucose were 1.19%, 1.09%, 0.71%, and 0.83%, respectively, while the inter-assay CVs were 1.49%, 1.71%, 1.80%, and 2.25%, respectively. These values demonstrate the acceptable precision and reliability of the biochemical measurements.

### Secondary endpoint

**Nutritional status and body composition.** The weight parameter was measured using a body impedance analysis (BIA) body fat analyser (OMRON HBF-375 Karada Scan, Japan). BIA

**Table 1** Diagnostic criteria and definition of MetS

Clinical measure	NCEP ATP-III Any three of the following five features:
Dyslipidemia	<input type="checkbox"/> TG >1.69 mmol L <sup>-1</sup> , or on pharmacological treatment <input type="checkbox"/> HDL-C (<1.13 mmol L <sup>-1</sup> for males; <1.3 mmol L <sup>-1</sup> for females), or on pharmacological treatment
Blood pressure	<input type="checkbox"/> ≥130/85 mmHg, or on pharmacological treatment
Plasma glucose	<input type="checkbox"/> ≥5.6 mmol L <sup>-1</sup> , or on pharmacological treatment
Central obesity	<input type="checkbox"/> WC (>102 cm for males; >88 cm for females)

TG = triglyceride; HDL-C = high density lipoprotein-cholesterol; WC = waist circumference.



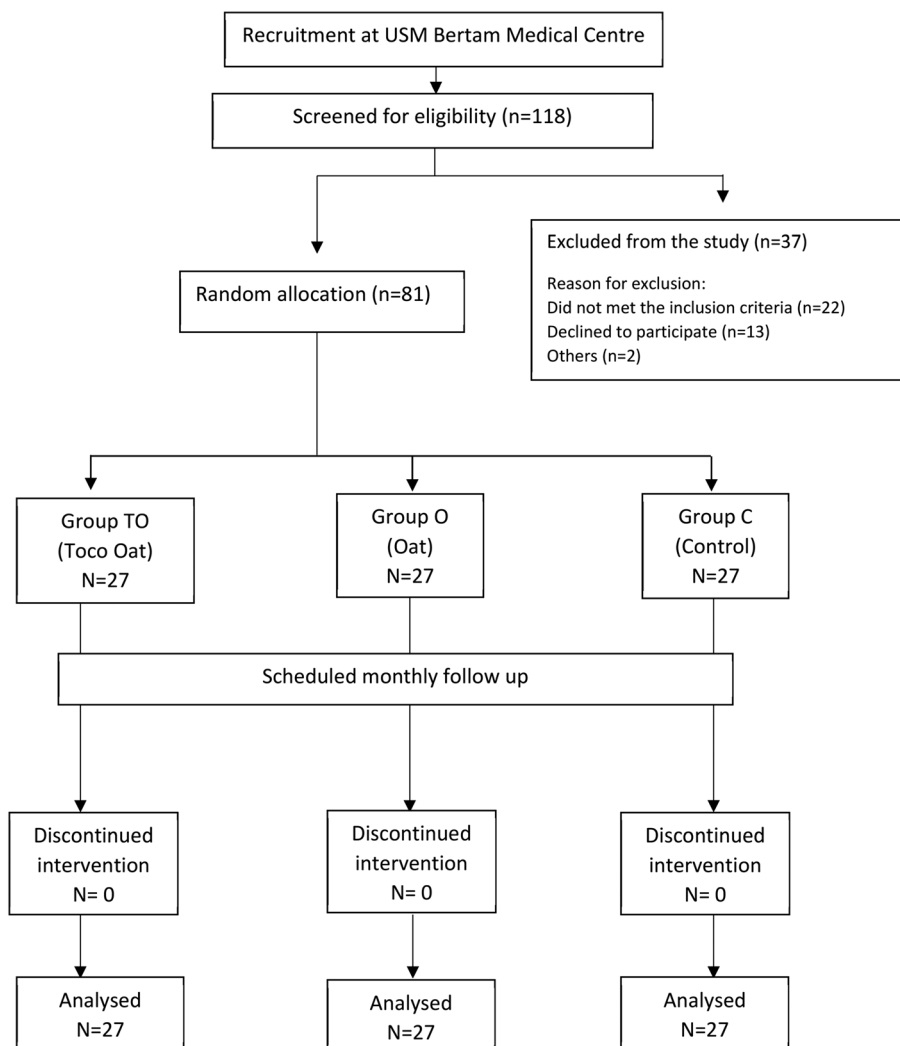


Fig. 1 Flowchart of the trial.

is a cost-effective and non-invasive alternative to dual-energy X-ray absorptiometry (DXA), the gold standard for body composition assessment.<sup>34</sup> However, BIA may underestimate body fat percentage, especially in overweight and obese individuals, and its performance can vary based on age, sex, and health status.<sup>35–38</sup> In the current study, the device was considered precise with the intra-unit coefficients of variation (CVs) of 5.6% (body fat), 2.3% (skeletal muscle mass) and 0.2% (visceral fat). Subjects were reminded to refrain from eating or engaging in strenuous exercise before the measurements. They were instructed to dress lightly, be under well-hydrated circumstances, empty bladders and remove all personal belongings that could significantly affect their weight. The body composition measurements included BMI, trunk measurements (waist and hip circumferences) and limb measurements (mid-upper arm and calf circumferences). The measurements were recorded in centimetres (cm) to the nearest 0.1 cm using a standard anthropometric measuring tape (SECA 201, China). Prior to the measurements, all anthropometric instruments

were calibrated to ensure the reproducibility of the anthropometric readings. All measurements were taken thrice based on the standard techniques. BMI was calculated as  $\text{kg m}^{-2}$  and classified into four categories: underweight ( $<18.5 \text{ kg m}^{-2}$ ), normal ( $18.5\text{--}24.9 \text{ kg m}^{-2}$ ), overweight ( $25.0\text{--}29.9 \text{ kg m}^{-2}$ ), and obese ( $\geq 30 \text{ kg m}^{-2}$ ).<sup>39</sup>

**Dietary intake.** Dietary assessment was conducted at the baseline and at the end of the study to determine the changes of dietary intake. Nutritional intake was compared at the baseline and after 12 weeks of intervention using the Dietary History Questionnaire (DHQ).<sup>40</sup> The DHQ was precoded and formatted, where detailed instructions and guidelines for the interviewers were included using non-leading and open-ended questions. The nutrient composition data were analysed using Nutritionist Pro™ software (version 7.9).

**Quality of life.** The EQ-E5 is a non-disease-specified generic health status questionnaire comprising a descriptive system (the index score) and a visual analogue scale (VAS). The descriptive system was used to assess the health status in five



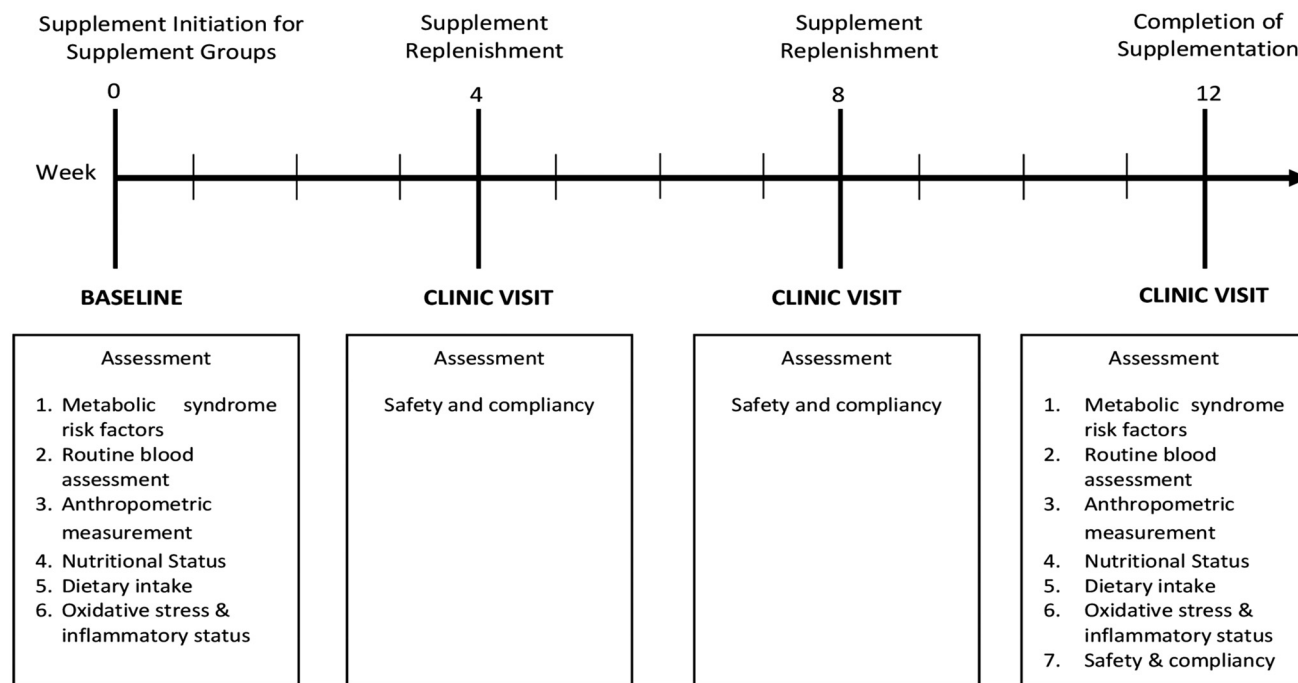


Fig. 2 Schematic diagram of the trial administration.

dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with scores ranging from no problems (1) to extreme problems (5).<sup>41</sup> The self-reported score reflects an individual's impression of their health status.<sup>42</sup> Thus, state 11111 reflects no problem in any dimension, while state 55555 reflects extreme problems in all five dimensions. The EQ-VAS is used for the self-assessment of health status, spanning from the 0 "worst imaginable health state" to 100 "best imaginable health state".

The country-specific value set is the prerequisite criterion for calculating health utility based on responses to the EQ-5D instruments. The Malaysian EQ-5D value set was utilized to compute values for all health states, ranging from −0.442 to 1.<sup>43</sup> The initial version of the tool had a value ranging from 0 to 1, where 0 represents death and 1 denotes total health. The EQ-5D-5L is a standardized protocol comprising 5 levels (5L) of answers. It is more preferred than 3-level answers (EQ-5D-3L), as the latter type suffers from substantial variation in elicitation methods.<sup>43</sup> The Malay version of the EQ-5D-5L was obtained from EuroQol (<https://www.euroqol.org>), and the implementation of the EQ-E5-5L (Malay version) was registered with EuroQol for research purposes.

**Ethical clearance.** The present study was conducted in accordance with the guidelines laid down in the Declaration of Helsinki, and the protocol involving human subjects has been approved by the Human Research Ethics Committee of Universiti Sains Malaysia (JEPeM) (code no: USM/JEPeM/22020101). This clinical trial has been registered in the clinical trial registry (ClinicalTrials.gov) with the registration ID NCT05604300. All patients signed an informed consent form prior participation.

**Statistical analysis.** All statistical analyses were implemented using version 27.0 of the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL) software. Normality was checked by using the Shapiro–Wilk test and by inspecting the scatterplots. The results are presented as the mean ± standard deviation or as the median (interquartile range). A paired *t*-test and McNemar's test, as appropriate, were used to assess the changes from the baseline to post-intervention within the same intervention group. We analysed the primary and secondary outcome measures by means of general linear model repeated-measures ANOVAs, with the three groups as between-subject factors and the two evaluations (baseline and post-intervention) as within-subject factors.

## Results

### Baseline characteristics

Out of 118 screened patients, 81 fulfilled the inclusion and exclusion criteria. All recruited subjects completed the trial. The study adherence rate was 91%, indicating that in overall, all subjects consumed 91% of the prescribed sachets. The baseline characteristics of the subjects are shown in Table 2. The median age was 61 years (36–78 years), and 53.1% of them were male. We did not find any significant difference with respect to the baseline characteristics among the three groups. In terms of tolerability, no serious adverse event was reported, and the side effects were mild. 3 subjects (3.7%) in the TO group and 2 subjects (2.5%) in the O group reported having bloated episodes during the early supplementation period.





Table 2 Baseline characteristics

Characteristics	Total ( <i>n</i> = 81)	Tocotrienol-enriched oat (TO) ( <i>n</i> = 27)	Oat (O) ( <i>n</i> = 27)	Control (C) ( <i>n</i> = 27)	<i>p</i>
Age (years)	59.3 ± 9.4	57.0 ± 9.3	61.8 ± 6.6	59.1 ± 11.2	0.162
Age group					0.242
≤60 years old	34 (42.0)	14 (51.9)	8 (29.6)	12 (44.4)	
>60 years old	47 (58.0)	13 (48.1)	19 (70.4)	15 (55.6)	
Gender					0.952
Male	43 (53.1)	15 (55.6)	14 (51.9)	14 (51.9)	
Female	38 (46.9)	12 (44.4)	13 (48.1)	13 (48.1)	
Race					0.402
Malay	76 (93.9)	26 (96.3)	25 (92.6)	25 (92.6)	
Indian	4 (4.9)	0 (0.0)	2 (7.4)	2 (7.4)	
Chinese	1 (1.2)	1 (3.7)	0 (0.0)	0 (0.0)	
Education attainment					0.317
Primary	5 (6.2)	3 (11.1)	1 (3.8)	1 (3.7)	
Secondary	47 (58.0)	15 (55.6)	13 (48.1)	19 (70.4)	
Tertiary	29 (35.8)	9 (33.3)	13 (48.1)	7 (25.9)	
Physical activity					0.142
Yes	45 (55.6)	19 (70.4)	14 (51.9)	12 (44.4)	
No	36 (44.4)	8 (29.6)	13 (48.1)	15 (55.6)	
Smoking					0.223
Yes	9 (11.1)	3 (11.1)	1 (3.7)	5 (18.5)	
No	72 (88.9)	24 (88.9)	26 (96.3)	22 (81.5)	
Medication prescription					0.746
Antidiabetic	69 (85.2)	24 (88.9)	23 (85.2)	22 (81.5)	
Antihypertensive	66 (81.5)	21 (77.8)	27 (100.0)	26 (96.3)	0.008
Hyperlipidemic	66 (81.5)	22 (81.5)	22 (81.5)	22 (81.5)	1.000
Metabolic profile					0.514
WC (cm)	100.8 ± 11.4	102.0 ± 9.1	98.7 ± 13.3	101.6 ± 11.6	
SBP (mmHg)	140.9 ± 17.1	148.7 ± 19.7	147.1 ± 17.9	140.9 ± 17.1	0.252
DBP (mmHg)	81.2 ± 9.7	82.9 ± 9.8	80.4 ± 10.1	80.2 ± 9.3	0.507
HDL-C (mmol L <sup>-1</sup> )	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	0.698
TG (mmol L <sup>-1</sup> )	1.6 ± 0.3	1.7 ± 0.8	1.6 ± 0.9	1.5 ± 0.4	0.575
FBG (mmol L <sup>-1</sup> )	7.3 ± 2.3	7.4 ± 2.4	7.5 ± 3.0	7.0 ± 1.3	0.761
Nutritional assessment					0.977
Height (cm)	158.9 ± 9.7	158.6 ± 12.7	159.2 ± 9.2	158.9 ± 9.7	
Weight (kg)	75.4 ± 14.0	77.5 ± 11.4	73.4 ± 15.1	75.2 ± 15.5	0.574
BMI (kg m <sup>-2</sup> )	30.0 ± 6.8	31.6 ± 9.6	28.8 ± 4.4	29.6 ± 5.2	0.305
Waist-hip ratio	0.94 ± 0.1	0.95 ± 0.1	0.92 ± 0.1	0.96 ± 0.1	0.073
MUAC (cm)	32.4 ± 7.2	31.8 ± 3.8	33.8 ± 11.4	31.7 ± 3.8	0.494
CC (cm)	37.1 ± 4.5	38.5 ± 3.1	36.3 ± 4.2	36.5 ± 5.5	0.129
Body composition					0.927
Body fat (%)	34.9 ± 5.5	34.7 ± 5.9	35.2 ± 6.0	34.8 ± 4.8	
Muscle mass (%)	24.3 ± 3.2	25.0 ± 3.4	23.7 ± 3.5	24.2 ± 2.5	0.315
Visceral fat (%)	16.2 ± 6.3	16.6 ± 5.4	15.9 ± 6.5	16.0 ± 7.1	0.919
Hand grip strength (kg)	22.5 ± 9.7	23.9 ± 9.0	21.6 ± 11.1	22.1 ± 8.9	0.656

Results are presented as mean ± SD or *n* (%). WC = waist circumference; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL-C = high density lipoprotein-cholesterol; TG = triglyceride; FBG = fasting blood glucose; MUAC = mid-upper arm circumference; CC = calf circumference.

### Prevalence and remission of MetS

The prevalence of MetS according to the diagnostic criteria is summarized in Table 3. Following the 12-week intervention, significant improvement in the prevalence of MetS was evident in the TO (−29.6%) and O (−14.8%) groups, respectively. MetS is considered to have remitted when, according to the NCEP ATP-III, only up to two of the components were present upon the second assessment.<sup>44</sup> The remission rate of MetS in the TO group was approximately twice that of the C group (37.0% vs. 18.5%). Specifically, the remission of MetS in the TO recipients increased five-fold after the intervention (7.4% to 37.0%), while in the O group, it increased from 18.5% to 33.3%. No remission was observed in the C group, with its rate remaining at 18.5%.

### Mean changes in MetS components

The estimated mean changes (pre- and post-measures) for MetS components of the three groups are depicted in Fig. 3. All MetS components showed significant improvements (*p* < 0.05), except for WC. Overall, the TO and O groups demonstrated decreasing trends in the BP, FBG, and TG levels (*p* < 0.05) and an increasing trend in the HDL-C levels (*p* < 0.05). Conversely, the C group exhibited contradictory trends.

### Changes in metabolic parameters

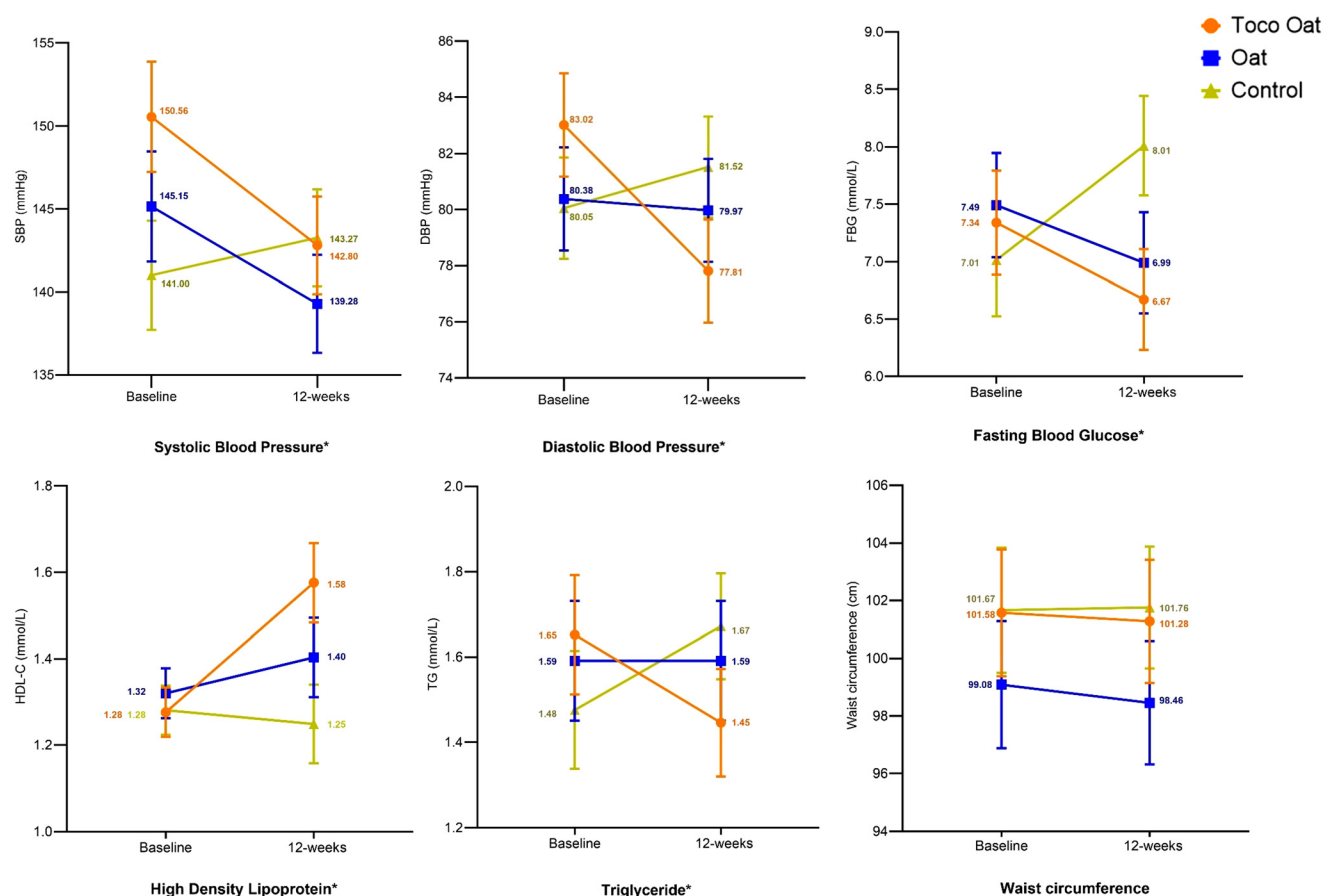
Further exploration revealed significant TO intervention effects on SBP (*F* = 4.017, *p* < 0.05,  $\eta^2$  = 0.096), DBP (*F* = 6.329, *p* < 0.01,  $\eta^2$  = 0.143), FBG (*F* = 5.961, *p* < 0.01,  $\eta^2$  = 0.136), HDL-C (*F* = 5.961, *p* < 0.05,  $\eta^2$  = 0.085), and TG (*F* = 5.380, *p* < 0.01,



**Table 3** Comparison of the prevalence of each component of MetS at the baseline and at the end of the intervention

Metabolic characteristics	Group TO ( <i>n</i> = 27)		Group O ( <i>n</i> = 27)		Group C ( <i>n</i> = 27)	
	Pre	Post	Pre	Post	Pre	Post
Overall prevalence	25 (92.6)	17 (63.0)	22 (81.5)	18 (66.7)	22 (81.5)	22 (81.5)
Abdominal obesity	24 (88.9)	25 (92.6)	25 (92.6)	24 (88.9)	26 (96.3)	27 (100.0)
Elevated TG	9 (33.3)	7 (25.9)	7 (25.9)	6 (22.2)	9 (33.3)	10 (37.0)
Reduced HDL-C	10 (37.0)	6 (22.2)	7 (25.9)	9 (33.3)	10 (37.0)	8 (29.6)
Elevated FBG	19 (70.4)	18 (66.7)	21 (77.8)	21 (77.8)	23 (85.2)	23 (85.2)
Elevated SBP	21 (77.8)	15 (55.6)	22 (81.5)	19 (70.4)	19 (70.4)	19 (70.4)
Elevated DBP	13 (48.1)	5 (18.5)	10 (37.0)	7 (25.9)	9 (33.3)	11 (40.7)
Remission rate (%) (pre vs. post)	7.4 vs. 37.0		18.5 vs. 33.0		18.5 vs. 18.5	

Results are shown as *n* (%). TG = triglyceride; HDL-C = high density lipoprotein; FBG = fasting blood glucose; SBP = systolic blood pressure; DBP = diastolic blood pressure.

**Fig. 3** Mean changes in the MetS components. \*Statistically significant difference: *p* < 0.05.

$\eta^2 = 0.124$ ) (Table 4). *Post hoc* analysis of pairwise differences and planned contrasts revealed no significant differences in SBP, DBP, or TG. Notably, significant differences in FBG were detected, with TO recipients reporting a lower FBG level than those in the C group after 12 weeks of supplementation (mean difference:  $-1.339 \text{ mmol L}^{-1}$ , *p* < 0.05). Similarly, the HDL-C level was significantly greater in the TO group than in the C group (mean difference:  $0.326 \text{ mmol L}^{-1}$ , *p* < 0.05), but no significant differences were detected between the TO and O groups, and between the O and C groups.

### Changes in the nutritional status

The dietary intake of energy, carbohydrate, protein, and fat, as determined by DHQ did not differ between the three groups (Table 5).

In terms of nutritional status, body fat percentage (*F* = 3.860, *p* < 0.05,  $\eta^2 = 0.093$ ) and muscle mass percentage (*F* = 3.237, *p* < 0.05,  $\eta^2 = 0.045$ ) exhibited significant intervention effects (Table 6). Body fat percentage showed significant reduction among those receiving TO ( $-0.7\%$ ) and showed an



**Table 4** Changes in the metabolic parameters

Parameter	Baseline	Post intervention	<i>F</i>	<i>p</i>	Partial $\eta^2$ squared, $\eta^2$
WC (cm)			0.310	0.734	0.008
Group TO	101.6 (2.2)	101.3 (2.1)			
Group O	99.1 (2.2)	98.5 (2.1)			
Group C	101.7 (2.17)	101.8 (2.1)			
SBP (mmHg)			4.017	0.022*	0.096
Group TO	150.6 (3.3)	142.8 (3.0)			
Group O	145.1 (3.3)	139.3 (3.0)			
Group C	141.0 (3.3)	143.3 (2.9)			
DBP (mmHg)			6.329	0.003**	0.143
Group TO	83.0 (1.8)	77.808 (1.8)			
Group O	80.4 (1.8)	79.970 (1.8)			
Group C	80.1 (1.8)	81.519 (1.8)			
HDL-C (mmol L <sup>-1</sup> )			5.96	0.034* <sup>+</sup>	0.085
Group TO	1.3 (0.1)	1.6 (0.092)			
Group O	1.3 (0.1)	1.40 (0.092)			
Group C	1.3 (0.1)	1.3 (0.091)			
TG (mmol L <sup>-1</sup> )			5.380	0.007**	0.124
Group TO	1.7 (0.140)	1.4 (0.126)			
Group O	1.6 (0.140)	1.6 (0.140)			
Group C	1.5 (0.138)	1.7 (0.124)			
FBG (mmol L <sup>-1</sup> )			5.961	0.004*** <sup>+</sup>	0.136
Group TO	7.3 (0.5)	6.7 (0.438)			
Group O	7.5 (0.5)	7.0 (0.439)			
Group C	7.0 (0.5)	8.0 (0.433)			

Data were adjusted for age, gender, medications, physical activity and energy intake. Results are expressed as mean (SEM). \* $p < 0.05$ ; \*\* $p < 0.01$ . <sup>+</sup>Indicates significant pairwise comparisons. WC = waist circumference; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL-C = high density lipoprotein-cholesterol; TG = triglyceride; FBG = fasting blood glucose.

**Table 5** Dietary intake changes at the baseline and after intervention

Characteristics	Baseline	Post intervention	<i>p</i>
Macronutrient			
Energy (kcal d <sup>-1</sup> )			
Group TO	1464.7 ± 275.8	1529.2 ± 266.2	0.060
Group O	1504.3 ± 278.4	1502.0 ± 294.9	0.928
Group C	1638.5 ± 369.5	1628.8 ± 372.3	0.778
Protein (g)			
Group TO	61.8 ± 16.5	66.7 ± 13.8	0.219
Group O	65.8 ± 13.8	63.0 ± 13.8	0.445
Group C	66.9 ± 16.8	69.0 ± 23.3	0.622
Carbohydrate (g)			
Group TO	200.3 ± 42.1	2009.7 ± 52.2	0.250
Group O	205.5 ± 29.0	217.1 ± 50.5	0.142
Group C	236.5 ± 62.9	233.5 ± 63.1	0.757
Fat (g)			
Group TO	46.3 ± 15.9	47.3 ± 11.8	0.778
Group O	46.5 ± 12.4	42.7 ± 13.7	0.175
Group C	47.3 ± 18.7	46.6 ± 18.2	0.877

Results are shown as mean ± SD.

increase in muscle mass (+0.3%), while the C group showed a paradoxical trend. However, further *post hoc* analysis did not reveal any significant pairwise mean differences between any pair of groups.

### Changes in quality of life

Overall, 11% of the subjects had satisfactory health-related QoL (coded as 11111 for all five dimensions). The McNemar test showed that none of the dimensions within the group had significant paired categorical data (baseline vs. post-treat-

ment). Subjects reported having the least problems in self-care (28.3%), and the dimensions of pain and discomfort were highly reported among the subjects (76.5%) (Table 7).

The subjects had an overall mean EQ-5D index or utility score of 0.786 and a mean EQ-VAS score of 83.76 at the baseline. The highest EQ-5D index score of 1 was reported at 11%, whereas the highest and lowest EQ-VAS scores were 92 and 50, respectively. Table 8 shows that both the TO and O groups reported significant improvements in the EQ-5D utility score and VAS score, while the scores were significantly lowered in the C group at the end of the intervention ( $p < 0.05$ ).

GLM-ANOVA revealed that there were significant intervention effects on the EQ-5D utility score ( $F = 3.371$ ,  $p < 0.05$ ,  $\eta^2 = 0.082$ ) and the VAS score ( $F = 19.521$ ,  $p < 0.01$ ,  $\eta^2 = 0.342$ ), indicating that the effectiveness of the interventions varied across the three treatment groups over time. *Post hoc* tests revealed significant differences between the treatment groups post-intervention, with the TO group showing a greater improvement than the C group (mean difference = 5.251,  $p < 0.05$ ) and the O group showing a greater improvement than the C group (mean difference = 4.132,  $p < 0.05$ ).

## Discussions

### Metabolic parameters

This was the first randomized, double-blind, placebo-controlled trial to investigate the functional capability of tocotrienol-enriched oat consumption for 12 weeks to affect the meta-





**Table 6** Mean changes in the nutritional status

Parameter	Baseline	Post intervention	<i>F</i>	<i>p</i>	Partial ETA squared, $\eta^2$
Body mass index (kg m <sup>-2</sup> )			1.567	0.216	0.040
Group TO	31.3 (1.3)	31.3 (1.4)			
Group O	29.1 (1.3)	29.5 (1.4)			
Group C	29.6 (1.3)	29.7 (1.4)			
Calf circumference (cm)			6.973	0.200	0.157
Group TO	38.1 (0.8)	36.035 (0.9)			
Group O	36.7 (0.8)	37.115 (0.9)			
Group C	36.5 (0.8)	36.869 (0.9)			
Upper arm circumference (cm)			1.006	0.370	0.026
Group TO	31.9 (1.4)	31.6 (2.5)			
Group O	33.7 (1.4)	33.5 (2.5)			
Group C	31.6 (1.4)	34.7 (2.5)			
Hip circumference (cm)			1.406	0.252	0.036
Group TO	107.5 (1.8)	106.0 (2.0)			
Group O	107.5 (1.8)	106.5 (2.0)			
Group C	105.7 (1.8)	105.4 (1.9)			
Waist to hip ratio			0.479	0.621	0.013
Group TO	0.9 (0.0)	1.0 (0.0)			
Group O	0.9 (0.0)	0.9 (0.0)			
Group C	1.0 (0.0)	1.0 (0.0)			
Body composition analysis					
Body fat (%)			3.860	0.025*	0.093
Group TO	35.1 (0.8)	34.4 (0.7)			
Group O	34.9 (0.8)	34.8 (0.7)			
Group C	34.7 (0.7)	35.5 (0.7)			
Muscle mass (%)			3.237	0.045*	0.079
Group TO	24.7 (0.3)	25.0 (0.3)			
Group O	24.0 (0.3)	24.5 (0.3)			
Group C	24.3 (0.3)	24.0 (0.3)			
Visceral fat			1.052	0.354	0.027
Group TO	16.4 (1.13)	16.5 (1.2)			
Group O	16.0 (1.13)	16.8 (1.2)			
Group C	16.1 (1.11)	16.6 (1.2)			
Hand grip strength (kg)			1.276	0.285	0.033
Group TO	23.1 (1.2)	23.7 (1.2)			
Group O	22.2 (1.2)	23.8 (1.2)			
Group C	22.2 (1.2)	21.9 (1.2)			

Data were adjusted for age, gender, medications, physical activity and energy intake. Results are expressed as mean (SEM). \**p* < 0.05.

**Table 7** Quality of life changes according to the treatment groups

Dimension	Group TO		Group O		Group C	
	Baseline <i>N</i> (%)	Post intervention <i>N</i> (%)	Baseline <i>N</i> (%)	Post intervention <i>N</i> (%)	Baseline <i>N</i> (%)	Post intervention <i>N</i> (%)
Mobility						
No problem	14 (51.9)	14 (51.9)	8 (29.6)	9 (33.3)	10 (37.0)	10 (37.0)
Slight to severe problem	13 (48.1)	13 (48.1)	19 (70.4)	18 (66.7)	17 (63.0)	17 (63.0)
Self-care						
No problem	19 (70.4)	22 (81.5)	20 (74.1)	22 (81.5)	19 (70.4)	23 (85.2)
Slight to severe problem	8 (29.6)	5 (18.5)	7 (25.9)	5 (18.5)	8 (29.6)	4 (14.8)
Usual activities						
No problem	12 (44.4)	14 (51.9)	7 (25.9)	6 (22.2)	10 (37.0)	8 (29.6)
Slight to severe problem	15 (55.6)	13 (48.1)	20 (74.1)	21 (77.8)	17 (63.0)	19 (70.4)
Pain/discomfort						
No problem	7 (25.9)	11 (40.7)	5 (18.5)	7 (25.9)	7 (25.9)	7 (25.9)
Slight problem	20 (74.1)	16 (59.3)	22 (81.5)	20 (74.1)	20 (74.1)	20 (74.1)
Anxiety/depression						
No problem	14 (51.9)	16 (59.3)	13 (48.1)	17 (63.0)	9 (33.3)	9 (33.3)
Slight problem	13 (48.1)	11 (40.7)	14 (51.9)	10 (37.0)	18 (66.7)	18 (66.7)

Results are presented as *n* (%).



**Table 8** Evaluation of the utility score and VAS

Parameter	Baseline	Post intervention	Mean change	<i>t</i> -Statistics	<i>p</i>
EQ-5D health utility					
Group TO	0.81 ± 0.14	0.85 ± 0.13	0.040	4.167	<0.0001*
Group O	0.77 ± 0.13	0.80 ± 0.12	0.035	3.828	<0.0001*
Group C	0.78 ± 0.13	0.78 ± 0.13	0.000	0.030	0.976
VAS score					
Group TO	73.81 ± 9.84	79.89 ± 7.3	6.074	5.719	<0.0001*
Group O	72.26 ± 8.98	76.67 ± 7.13	4.407	5.894	<0.0001*
Group C	74.67 ± 7.77	73.70 ± 7.50	−0.963	−1.701	0.101

Results are expressed as mean ± SD. A paired *t*-test was used. Cohen's *d* was used to estimate the effect size. \*Significant difference at *p* < 0.0001.

bolic profile, nutritional status and QoL among individuals with MetS. Given the significant MetS complications within the population, there is a need to frame the evidence-based strategies for safe secondary prevention. Trial adherence was satisfactory, with minimal gastrointestinal complaints. There were no severe adverse events, and the side effects were minimal and transient. In this study, the remission rate of MetS in the subjects receiving TO was approximately twice that in the C group. We hereby suggest that the provision of tocotrienol-enriched oats improved MetS parameters, including BP, TG, HDL-C, and FBG levels.

The administration of 100 mg d<sup>−1</sup> tocotrienol incorporated into oats for 12 weeks reduced FBG by 4.5% among individuals with MetS. A 15.4% reduction in FBG was reported among individuals supplemented with tocotrienol-enriched canola oil for 8 weeks.<sup>45</sup> Differences in glucose concentrations at the baseline may be a determinant of the response to tocotrienol supplementation and the rate of FBG reduction.<sup>45</sup> The hypoglycemic effect of tocotrienol is more likely to be observed in individuals with higher FBG concentrations or poorer glycemic indices at the baseline. The subjects in our study exhibited lower and more controlled baseline FBG levels than those in previously reported studies,<sup>45</sup> which partly explains the modest improvement in FBG after the intervention. The mechanism underlying the effect of tocotrienol on glycemic control is still unclear. The most frequently discussed pathway is the anti-oxidative action of tocotrienol, which protects pancreatic beta cells from oxidative damage, primarily attributed to its insulinotropic<sup>46</sup> and insulin-sensitizing activities.<sup>47</sup> Although both animal and human studies reported an improvement in glucose homeostasis following tocotrienol supplementation,<sup>48</sup> other studies have reported contradicting results.<sup>49,50</sup> We postulate that such discrepancy could be due to the variations in tocotrienol dosage, the administration of different potent isomers, and the duration of the intervention period. According to Chia *et al.* (2016), T3 isoforms, such as α-T3, γ-T3, and δ-T3, exhibit insulinotropic effects, with δ-T3 being the most potent, followed by γ-T3 and α-T3.<sup>51</sup> Moreover, the effective dose required for optimal effects remains uncertain. One preliminary study revealed that tocotrienol dosage from 100 mg d<sup>−1</sup> to 960 mg d<sup>−1</sup> was useful for cardiovascular protection.<sup>52</sup>

Glucose-lowering effects were also observed among the subjects receiving oat supplementation, and with the addition of

tocotrienol, the FBG was further reduced by 0.5% (4.5%) compared to the subjects receiving oats alone (4.0%). Few human trials and animal studies have reported improvement in the FBG level with the intake of oats;<sup>6,53</sup> however, few randomized controlled trials corroborated these findings.<sup>54,55</sup> The consumption of greater doses of β-glucan or smaller doses of β-glucan for longer periods of time may produce better results.<sup>4,38,56</sup> In another clinical trial, a 12-week administration of 3.0 g of β-glucan per person resulted in a reduction in glycaemia<sup>57</sup> compared to that in the control group, with similar dosages for 4 weeks<sup>58</sup> or 3.5 g per person per d for 8 weeks<sup>59</sup> being deemed ineffective. These findings suggest that a longer duration of intervention involving the use of oats as an active treatment for more than 8 weeks is suggested to improve the glycemic marker levels.

We highlight the significant reductions in SBP and DBP in the TO group compared to those in the O and C groups. Studies have described a contradictory pattern of systolic and diastolic patterns following supplementation with tocotrienol. In 2022, Li and colleagues inferred that the administration of tocotrienol resulted in significant reduction in SBP, but no discernible improvement in DBP.<sup>60</sup> Our data revealed an improvement in overall BP among those who received tocotrienol-enriched oats or oats alone, further corroborating the earlier studies.<sup>44,45,61</sup> The mechanism through which tocotrienol enhances nitric oxide (NO) production has been identified as a pivotal pathway. Tocotrienol exerts its influence by bolstering the activity of NO synthase, thereby augmenting the production of NO. NO is a vasodilator that facilitates blood vessel relaxation and dilation, directly enhances blood circulation and reduces resistance to BP.<sup>62</sup>

This study revealed a significant 3.9% reduction in SBP in subjects receiving oats, while no effects on DBP were reported, corroborating a recent meta-analysis.<sup>63</sup> However, few other studies have reported contradictory results.<sup>64,65</sup> Subgroup analyses of baseline SBP showed that oat consumption significantly reduced SBP in patients with hypertension or in the prehypertensive state, indicating that prominent antihypertensive effects might be dependent on the baseline BP levels.<sup>63,66</sup> Oat β-glucan is fermented by the gut microbiota to increase the production of short-chain fatty acids (SCFAs). SCFAs are the main elements involved in BP reduction, primarily by activating transmembrane G protein-coupled receptors and inhibiting



ing histone acetylation.<sup>67</sup> Additionally, oat  $\beta$ -glucan favourably modulates the gut microbiota by selectively promoting the growth of *Bifidobacterium* and *Lactobacillus* spp., which further help regulate BP levels.<sup>68</sup>

The addition of tocotrienol to oats further amplified the beneficial impact on HDL-C by 34.1%, and reduced TG by 7.1%. An increase in HDL-C and a decrease in TG in patients receiving tocotrienol supplements have been consistently reported previously,<sup>27,50</sup> and an increase in HDL-C was more apparent in patients receiving tocotrienol dosages  $\geq 200$  mg d<sup>-1</sup>.<sup>23</sup> The effect of tocotrienol on cholesterolemia may be attributed to a possible increase in the concentration of ApoA1, the major protein component of HDL-C particles.<sup>69</sup> Heng and colleagues reported an increase in the expression of ApoA1 and the ApoE precursor and downregulation of the C-reactive protein (CRP) among individuals receiving tocotrienol.<sup>70</sup> The finding implied that tocotrienol not only has a beneficial effect on plasma tocotrienol, but also modulates the expression of proteins that are beneficial against atherosclerosis. Mechanistically, tocotrienol downregulates the uptake of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and suppresses the production of mevalonate, the precursor molecule in the cholesterol biosynthesis pathway.<sup>62</sup> The combined action limits the synthesis of cholesterol,<sup>71</sup> further inhibiting cholesterol absorption in the intestine.<sup>72</sup>

Oat supplementation alone increased the HDL-C concentration (+3.0%), while no significant change was observed in the TG level. The beneficial effects of oats in reducing LDL-C and TC have been widely reported and supported by a few meta-analyses. However, little effect was observed on TG, HDL-C and major cardiovascular events among dyslipidaemia patients.<sup>73</sup> A previous study demonstrated that a hypocaloric diet supplemented with 6 g of  $\beta$ -glucan leads to a significant increase in HDL-C and a decrease in LDL-C.<sup>14</sup> Oats improve lipoprotein profiles by lowering fatty acid synthase (FAS), glycerol-3-phosphate acyltransferase (GPAT) and HMG CoA reductase, while promoting the expression of peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ), carnitine palmitoyl-transferase-1 (CPT-1) and AMP-activated protein kinase (AMPK).<sup>74</sup> Oats increase hepatic LDL receptor (LDLR) activity, which is accountable for eliminating LDL-C from the bloodstream and is thus beneficial for lipid clearance.

### Nutritional status and body composition

We did not find the beneficial effects of tocotrienol-enriched oat supplementation in terms of weight changes, BMI, or other anthropometric indicators, aligned with previous studies.<sup>25,75,76</sup> Similarly, daily consumption of oats did not influence the weight changes among overweight and diabetic individuals.<sup>19,20,59</sup> Earlier studies have reported significant reductions in weight, waist circumference, and BMI after oat consumption;<sup>18,53,77</sup> however, the outcome was primarily due to calorie deficit regimes.

Intriguingly, we demonstrated significant reduction in body fat percentage in the TO group compared to the O and C groups, which was also observed in animal studies.<sup>78–80</sup>

Tocotrienol is involved in the downregulation of PPAR $\gamma$ , the key mediator of lipogenesis,<sup>81</sup> and increases insulin sensitivity and repartitions lipids from fat storage (adipose tissue), potentially reducing fat accumulation.<sup>82</sup> The anti-adipogenic effects of tocotrienol depend on its homologues, with  $\gamma$ -tocotrienol exhibiting greater inhibitory effects on adipogenesis than  $\alpha$ -tocotrienol.<sup>83</sup> Tocotrienol, along with retinoids and carotenoids (ligands of retinoic acid X-receptor), is involved in the early stage of differentiation in 3T3-L1 preadipocytes,<sup>84</sup> suggesting that tocotrienols might suppress adipogenesis in preadipocytes but not adipocytes.<sup>83</sup> The O group did not exhibit significant reduction in body fat percentage after 12 weeks of intervention, which was corroborated with previous studies.<sup>17</sup> Maki and co-workers (2010) reported a significant reduction in abdomen fat among those receiving oat supplementation and was compounded with energy restriction ( $\sim 500$  kcal d<sup>-1</sup>).<sup>18</sup>

This study contributes valuable insights into the effects of tocotrienol-enriched oats in enhancing skeletal muscle mass. Our intervention agent included slightly lower dosages of tocotrienol (100 mg d<sup>-1</sup>) and  $\beta$ -glucan (3.6 g d<sup>-1</sup>). We postulate that the therapeutic effects of both tocotrienol and  $\beta$ -glucan may help to confirm these results. To date, limited studies have investigated the role of tocotrienol in skeletal muscle health, with most reports focusing on the provision of tocopherol among sarcopenic elderly individuals<sup>85</sup> and reversing muscle damage.<sup>86,87</sup> Under the pretext of adequate vitamin E levels, skeletal muscle mass may survive even with a massive production of reactive oxygen species (ROS) during muscle contraction due to its ability to repair the myoblast membrane.<sup>88</sup> This action is attributable to its natural lipid-soluble properties, which facilitate its entry to the hydrophobic core of the plasma membrane.

The evidence of oats and whole grains in improving skeletal muscle function among humans is limited. An observational study reported that adults who adopted a healthy diet rich in whole grains experienced improved muscle function, increased muscle mass and a reduced rate of sarcopenia.<sup>89</sup> Oat  $\beta$ -glucan inhibits the activity of creatine kinase and lactate dehydrogenase in serum, while increasing the glycogen content in the muscles, indicating the facilitation of recovery from fatigue.<sup>90</sup> Although studies have reported a potential role of oats in muscle recovery, the mechanism by which oat  $\beta$ -glucan enhances skeletal muscle mass remains unknown and therefore requires further investigation.

### Health-related quality of life

Pain and discomfort (PD) was frequently reported among MetS subjects. A study in Thailand revealed that more than half of the T2DM patients experienced issues with PD.<sup>91</sup> Similarly, a study in China revealed a strong association between reduced index health utility scores and problems in PD among T2DM patients.<sup>92</sup> In Singapore, a multi-ethnic study revealed that individuals of all races reported high levels of problems with physical dimension.<sup>93</sup> Previous study has reported the impact of MetS on HR-QoL,<sup>94</sup> while other did not find significant cor-



**Table 9** Changes of HR-QoL

Parameter	Baseline	Post intervention	<i>F</i>	<i>p</i>	Partial ETA squared, $\eta^2$
EQ5D utility score			3.371	0.040*	0.082
Group TO	0.78 ± 0.02	0.83 ± 0.02			
Group O	0.80 ± 0.02	0.83 ± 0.02			
Group C	0.78 ± 0.02	0.78 ± 0.02			
VAS score			19.521	<0.001**	0.342
Group TO	72.85 ± 1.52	78.88 ± 1.16			
Group O	73.30 ± 1.52	77.76 ± 1.16			
Group C	74.59 ± 1.49	73.63 ± 1.14			

Data were adjusted for age, gender, medications, physical activity and energy intake. Results are expressed as mean ± SD. \*Significant at  $p < 0.05$ ; \*\*significant at  $p < 0.001$ .

relation.<sup>95</sup> The disparity of the tools used in assessing HR-QoL and the various diagnostic criteria employed in identifying populations with MetS remain the major challenge in drawing such conclusions.

Health utility represents an individual's affinity for a given health state. A self-rated negative value of health utility is possible, suggesting that a health state is perceived as being worse than death.<sup>96</sup> This study revealed a significant improvement in health utility with the consumption of TO, while control subjects showed worse health utility over time. The health utility of MetS has not been widely reported, but instead, emphasis has mostly been placed on its impact on comorbidities such as T2DM and cardiovascular disease and hypertension.<sup>92,96</sup> We established a health utility value of 0.79 among individuals with MetS; 11% of the subjects had a full score, with the PD dimension being the most frequently reported problem. Both the TO and O interventions improved health utility and VAS scores, indicating that receiving supplements had a greater influence on HR-QoL. It is anticipated that people undergoing any health treatment will have an influence on their psychological perception and effects on their mental state.

To the best of our knowledge, this is the first human clinical trial to investigate the functionality of the combination of tocotrienol and oat consumption to ameliorate MetS. The strength of our study lies in its rigorous methodology, incorporating a double-blind randomized controlled design to ensure the robustness and reliability of the findings. Regular monthly follow-up allowed close monitoring of supplement adherence. We reported a high compliance rate towards the trial regime – 91%, illustrating the regulatory effects of the treatment given. We acknowledge the small sample size of this preliminary study, hence a larger study with a multi-centre design is suggested. In addition, a balanced proportion of patients with multiple ethnicities should be used to discern the possibility of racial disparity. We acknowledge the disadvantages of BIA in measuring body composition. In future, the use of DXA is highly recommended for precise clinical monitoring in overweight and obese populations. A single-time-point data collection may limit the ability to assess trends or changes over a longer period. Future studies with more frequent data collection points would provide more robust insights into the temporal effects of the interventions on MetS.

## Conclusion

MetS complicates health by interrelation between obesity, hypertension, insulin resistance, and dyslipidemia and a cluster of risk factors for cardiovascular disease and T2DM. The significant improvements observed in FBG, BP, HDL-C, TG, muscle mass and body fat suggest that tocotrienol-incorporated oat supplementation could be a valuable complementary medicine therapy to manage MetS. These findings support the notion that dietary interventions can play a crucial role in the comprehensive management of MetS, offering a safe and cost-effective strategy for secondary prevention. Further research is warranted to elucidate the underlying mechanisms and long-term effects of tocotrienol-enriched oat supplementation as a functional food in individuals with MetS.

## Author contributions

Conceptualization: Camilla Wahida Norazman, Mastura Mohd Sopian and Lai Kuan Lee. Study design: Camilla Wahida Norazman, Mastura Mohd Sopian and Lai Kuan Lee. Writing – original draft preparation: Camilla Wahida Norazman. Writing – review and editing: Camilla Wahida Norazman and Lai Kuan Lee. Supervision: Lai Kuan Lee and Mastura Mohd Sopian. Funding acquisition: Lai Kuan Lee. All authors have read and agreed to the published version of the manuscript.

## Data availability

Data collected from human participants, described in Tables 2–9, are not available publicly for confidentiality reasons. However, the data are available upon official request.

## Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



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## References

- 1 J. I. Cleeman, S. M. Grundy, D. Becker and L. Clark, Expert panel on detection, evaluation and treatment of high blood cholesterol in adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III), *J. Am. Med. Assoc.*, 2001, **285**(19), 2486–2497.
- 2 G. Ricci, I. Pirillo, D. Tomassoni, A. Sirignano and I. Grappasonni, Metabolic syndrome, hypertension, and nervous system injury: Epidemiological correlates, *Clin. Exp. Hypertens.*, 2017, **39**(1), 8–16. Available from: <https://www.tandfonline.com/doi/full/10.1080/10641963.2016.1210629>.
- 3 N. Steckhan, C.-D. Hohmann, C. Kessler, G. Dobos, A. Michalsen and H. Cramer, Effects of different dietary approaches on inflammatory markers in patients with metabolic syndrome: A systematic review and meta-analysis, *Nutrition*, 2016, **32**(3), 338–348. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0899900715004025>.
- 4 A. Amerizadeh, H. S. Ghaheh, G. Vaseghi, Z. Farajzadegan and S. Asgary, Effect of Oat (*Avena sativa* L.) Consumption on Lipid Profile With Focus on Triglycerides and High-density Lipoprotein Cholesterol (HDL-C): An Updated Systematic Review, *Curr. Probl. Cardiol.*, 2023, **48**(7), 101153. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0146280622000500>.
- 5 R. Mathews and A. C. Y. Kamil, Global review of heart health claims for oat beta-glucan products, *Nutr. Rev.*, 2020, **78**(Supplement\_1), 78–97, DOI: [10.1093/nutrit/nuz069](https://doi.org/10.1093/nutrit/nuz069).
- 6 X. Shen, T. Zhao, Y. Zhou, X. Shi, Y. Zou and G. Zhao, Effect of oat  $\beta$ -glucan intake on glycaemic control and insulin sensitivity of diabetic patients: A meta-analysis of randomized controlled trials, *Nutrients*, 2016, **8**(1), 39, DOI: [10.3390/nu8010039](https://doi.org/10.3390/nu8010039).
- 7 US Food and Drug Administration, Final rule for food labeling: health claims. Oats and coronary heart disease, Federal Register, 1997, vol. 62, pp. 3584.
- 8 Food and Drug Administration H, Food labeling: health claims; soluble fiber from certain foods and risk of coronary heart disease. Final rule, *Fed. Regist.*, 2008, **73**(85), 23947–23953. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/18567170>.
- 9 EFSA, Scientific Opinion on the substantiation of a health claim related to oat beta glucan and lowering blood cholesterol and reduced risk of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006, *EFSA J.*, 2010, **8**(12), 1885 <https://doi.wiley.com/10.2903/j.efsa.2010.1885>.
- 10 AFFSA, French Agency for Food Safety on the Application for Assessment of Scientific Basis for the Allegation to the Effect of Oat Soluble Fiber Consumed in an Adequate Diet on Blood Cholesterol, French Agency for Food, Environment and Occupational Health & Safety, 2008. Available from: <https://www.afssa.fr/documents/nut2007sa0168.pdf>.
- 11 JHC Initiative, Code of Practice on Health Claims on Foods, 2010. Available from: [https://webarchive.nationalarchives.gov.uk/ukgwa/20130418084330/https://www.food.gov.uk/multimedia/pdfs/jhci\\_healthreport.pdf](https://webarchive.nationalarchives.gov.uk/ukgwa/20130418084330/https://www.food.gov.uk/multimedia/pdfs/jhci_healthreport.pdf).
- 12 H. Canada, Oat Products and Blood Cholesterol Lowering: Summary of Assessment of a Health Claim about Oat Products and Blood Cholesterol Lowering. 2010. Available from: <https://www.canada.ca/en/health-canada/services/food-nutrition/food-labelling/health-claims/assessments/products-blood-cholesterol-lowering-summary-assessment-health-claim-about-products-blood-cholesterol-lowering.html>.
- 13 P. L. B. Holl  nder, A. B. Ross and M. Kristensen, Whole-grain and blood lipid changes in apparently healthy adults: a systematic review and meta-analysis of randomized controlled studies, *Am. J. Clin. Nutr.*, 2015, **102**(3), 556–572.
- 14 N. Reyna-Villasmil, V. Berm  dez-Pirela, E. Mengual-Moreno, N. Arias, C. Cano-Ponce, E. Leal-Gonzalez, *et al.*, Oat-derived  $\beta$ -Glucan Significantly Improves HDLC and Diminishes LDLC and Non-HDL Cholesterol in Overweight Individuals With Mild Hypercholesterolemia, *Am. J. Ther.*, 2007, **14**(2), 203–212. Available from: <https://journals.lww.com/00045391-200703000-00015>.
- 15 R. A. Othman, M. H. Moghadasian and P. J. Jones, Cholesterol-lowering effects of oat  $\beta$ -glucan, *Nutr. Rev.*, 2011, **69**(6), 299–309. Available from: <https://academic.oup.com/nutritionreviews/article-lookup/doi/10.1111/j.1753-4887.2011.00401.x>.
- 16 N. Gunness, J. Michiels, S. De Smet, L. Vanhaecke, O. Kravchuk, A. Van de Meene, *et al.*, Oat  $\beta$ -glucan lowers blood cholesterol by restricting its intestinal absorption and decreasing bile acids levels, *J. Nutr. Intermed. Metab.*, 2017, **8**, 80. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S2352385917300877>.
- 17 E. Saltzman, S. K. Das, A. H. Lichtenstein, G. E. Dallal, A. Corrales, E. J. Schaefer, *et al.*, An Oat-Containing Hypocaloric Diet Reduces Systolic Blood Pressure and Improves Lipid Profile beyond Effects of Weight Loss in Men and Women, *J. Nutr.*, 2001, **131**(5), 1465–1470. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0022316622138228>.
- 18 K. C. Maki, J. M. Beiseigel, S. S. Jonnalagadda, C. K. Gugger, M. S. Reeves, M. V. Farmer, *et al.*, Whole-Grain Ready-to-Eat Oat Cereal, as Part of a Dietary Program for Weight Loss, Reduces Low-Density Lipoprotein Cholesterol in Adults with Overweight and Obesity More than a Dietary Program Including Low-Fiber Control Foods, *J. Am. Diet. Assoc.*, 2010, **110**(2), 205–214. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0002822309018136>.
- 19 E. J. Beck, L. C. Tapsell, M. J. Batterham, S. M. Tosh and X.-F. Huang, Oat  $\beta$ -glucan supplementation does not enhance the effectiveness of an energy-restricted diet in overweight women, *Br. J. Nutr.*, 2010, **103**(8), 1212–1222.





- Available from: [https://www.cambridge.org/core/product/identifier/S0007114509992856/type/journal\\_article](https://www.cambridge.org/core/product/identifier/S0007114509992856/type/journal_article).
- 20 K. E. Charlton, L. C. Tapsell, M. J. Batterham, J. O'Shea, R. Thorne, E. Beck, *et al.*, Effect of 6 weeks' consumption of  $\beta$ -glucan-rich oat products on cholesterol levels in mildly hypercholesterolaemic overweight adults, *Br. J. Nutr.*, 2012, **107**(7), 1037–1047. Available from: [https://www.cambridge.org/core/product/identifier/S0007114511003850/type/journal\\_article](https://www.cambridge.org/core/product/identifier/S0007114511003850/type/journal_article).
  - 21 L. d. S. Leão, L. d. Aquino, J. F. Dias and R. J. Koifman, Addition of oat bran reduces HDL-C and does not potentiate effect of a low-calorie diet on remission of metabolic syndrome: A pragmatic, randomized, controlled, open-label nutritional trial, *Nutrition*, 2019, **65**, 126–130. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0899900718307883>.
  - 22 X. Li, X. Cai, X. Ma, L. Jing, J. Gu, L. Bao, *et al.*, Short- and Long-Term Effects of Wholegrain Oat Intake on Weight Management and Glucolipid Metabolism in Overweight Type-2 Diabetics: A Randomized Control Trial, *Nutrients*, 2016, **8**(9), 549. Available from: <https://www.mdpi.com/2072-6643/8/9/549>.
  - 23 S. Zuo, G. Wang, Q. Han, H. LeXiao, O. Santos, H. Avelar Rodriguez, *et al.*, The effects of tocotrienol supplementation on lipid profile: A meta-analysis of randomized controlled trials, *Complement. Ther. Med.*, 2020, **52**, 102450.
  - 24 E. Magosso, M. A. Ansari, Y. Gopalan, I. L. Shuaib, J.-W. Wong, N. A. K. Khan, *et al.*, Tocotrienols for normalisation of hepatic echogenic response in nonalcoholic fatty liver: a randomised placebo-controlled clinical trial, *Nutr. J.*, 2013, **12**(1), 166. Available from: <https://nutritionj.biomedcentral.com/articles/10.1186/1475-2891-12-166>.
  - 25 K. S. Heng, A. R. Hejar, J. Johnson Stanslas, C. P. Ooi and S. P. Loh, Potential of Mixed Tocotrienol Supplementation in Adults with Metabolic Syndrome, *Malays. J. Nutr.*, 2015, **22**(2), 231–243.
  - 26 M. A. Pervez, D. A. Khan, A. Ijaz and S. Khan, Effects of Delta-tocotrienol Supplementation on Liver Enzymes, Inflammation, Oxidative stress and Hepatic Steatosis in Patients with Nonalcoholic Fatty Liver Disease, *Turk. J. Gastroenterol.*, 2018, **29**(2), 170–176. Available from: <https://turkjgastroenterol.org/en/effects-of-delta-tocotrienol-supplementation-on-liver-enzymes-inflammation-oxidative-stress-and-hepatic-steatosis-in-patients-with-nonalcoholic-fatty-liver-disease-135243>.
  - 27 S. Fatima, D. A. Khan, M. Aamir, M. A. Pervez and F. Fatima,  $\delta$ -Tocotrienol in Combination with Resveratrol Improves the Cardiometabolic Risk Factors and Biomarkers in Patients with Metabolic Syndrome: A Randomized Controlled Trial, *Metab. Syndr. Relat. Disord.*, 2023, **21**(1), 25–34. Available from: <https://www.liebertpub.com/doi/10.1089/met.2022.0052>.
  - 28 P. Chedraui, L. Hidalgo, D. Chavez, M. Morocho, M. Alvarado and A. Huc, Quality of life among post-menopausal Ecuadorian women participating in a metabolic syndrome screening program, *Maturitas*, 2007, **56**(1), 45–53.
  - 29 E. S. Ford and C. Li, Metabolic Syndrome and Health-Related Quality of Life among U.S. Adults, *Ann. Epidemiol.*, 2008, **18**(3), 165–171. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1047279707004474>.
  - 30 I. S. Okosun, F. Annor, F. Esuneh and E. E. Okoegwale, Metabolic syndrome and impaired health-related quality of life and in non-Hispanic White, non-Hispanic Blacks and Mexican-American Adults, *Diabetes Metabolic Syndrome: Clinical Research & Reviews*, 2013, **7**(3), 154–160. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1871402113000659>.
  - 31 Y.-H. Lin, H.-T. Chang, Y.-H. Tseng, H.-S. Chen, S.-C. Chiang, T.-J. Chen, *et al.*, Changes in metabolic syndrome affect the health-related quality of life of community-dwelling adults, *Sci. Rep.*, 2021, **11**(1), 20267. Available from: <https://www.nature.com/articles/s41598-021-99767-y>.
  - 32 M. L. Vetter, T. A. Wadden, J. Lavenberg, R. H. Moore, S. Volger, J. L. Perez, *et al.*, Relation of health-related quality of life to metabolic syndrome, obesity, depression and comorbid illnesses, *Int. J. Obes.*, 2011, **35**(8), 1087–1094. Available from: <https://www.nature.com/articles/ijo2010230>.
  - 33 M. F. Barcones-Molero, A. Sánchez-Villegas, M. A. Martínez-González, M. Bes-Rastrollo, M. Martínez-Urbistondo, J. Santabábara, *et al.*, The influence of obesity and weight gain on quality of life according to the SF-36 for individuals of the dynamic follow-up cohort of the University of Navarra, *Rev. Clin. Esp.*, 2018, **218**(8), 408–416. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S225488741830122X>.
  - 34 A. Scafoglieri and J. P. Clarys, Dual energy X-ray absorptiometry: gold standard for muscle mass?, *J. Cachexia Sarcopenia Muscle*, 2018, **9**(4), 786–787. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/29786955>.
  - 35 N. Achamrah, G. Colange, J. Delay, A. Rimbart, V. Folope, A. Petit, *et al.*, Comparison of body composition assessment by DXA and BIA according to the body mass index: A retrospective study on 3655 measures, *PLoS One*, 2018, **13**(7), e0200465. Available from: <https://dx.plos.org/10.1371/journal.pone.0200465>.
  - 36 N. Dahlmann and V. Demond, A new anthropometric model for body composition estimation: Comparison with a bioelectrical impedance consumer device, *PLoS One*, 2022, **17**(9), e0271880. Available from: <https://dx.plos.org/10.1371/journal.pone.0271880>.
  - 37 J.-G. Wang, Y. Zhang, H.-E. Chen, Y. Li, X.-G. Cheng, L. Xu, *et al.*, Comparison of Two Bioelectrical Impedance Analysis Devices With Dual Energy X-ray Absorptiometry and Magnetic Resonance Imaging in the Estimation of Body Composition, *J. Strength Cond. Res.*, 2013, **27**(1), 236–243. Available from: <https://journals.lww.com/00124278-201301000-00033>.
  - 38 L. Xu, X. Cheng, J. Wang, Q. Cao, T. Sato, M. Wang, *et al.*, Comparisons of Body-Composition Prediction Accuracy: A Study of 2 Bioelectric Impedance Consumer Devices in Healthy Chinese Persons Using DXA and MRI as Criteria Methods, *J. Clin. Densitom.*, 2011, **14**(4), 458–464. Available



- from: <https://linkinghub.elsevier.com/retrieve/pii/S1094695011000837>.
- 39 World Health Organization W, Obesity: preventing and managing the global epidemic. Report of a WHO consultation, *World Health Organ. Tech. Rep. Ser.*, 2000, **894**(i–xii), 1–253. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/11234459>.
  - 40 S. Suzana, J. Earland and A. R. Suriah, Validation of a Dietary History Questionnaire against a 7-D Weighed Record for Estimating Nutrient Intake among Rural Elderly Malays, *Mal. J. Nutr.*, 2000, **6**(1), 33–44.
  - 41 N. Devlin, B. Roudijk and K. Ludwig, in *Value Sets for EQ-5D-5L*, ed. N. Devlin, B. Roudijk and K. Ludwig, Springer International Publishing, Cham, 2022. Available from: <https://link.springer.com/10.1007/978-3-030-89289-0>.
  - 42 D. K. Whynes, Correspondence between EQ-5D health state classifications and EQ VAS scores, *Health Qual. Life Outcomes*, 2008, **6**(1), 94. Available from: <https://hqlo.biomedcentral.com/articles/10.1186/1477-7525-6-94>.
  - 43 A. A. Shafie, A. Vasan Thakumar, C. J. Lim, N. Luo, K. Rand-Hendriksen, M. Yusof and F. A. EQ-5D-5L Valuation for the Malaysian Population, *Pharmacoeconomics*, 2019, **37**(5), 715–725. Available from: <https://link.springer.com/10.1007/s40273-018-0758-7>.
  - 44 K. Alberti, R. Eckel, S. Grundy, P. Zimmet, J. Cleeman, K. Donato, *et al.*, Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international, *Circulation*, 2009, **120**(16), 1640–1645.
  - 45 M. Vafa, N. Haghighat, N. Moslehi, S. Egtesadi and I. Heydari, Effect of Tocotrienols enriched canola oil on glycemic control and oxidative status in patients with type 2 diabetes mellitus: A randomized double-blind placebo-controlled clinical trial, *J. Res. Med. Sci.*, 2015, **20**(6), 540. Available from: <https://journals.lww.com/10.4103/1735-1995.165945>.
  - 46 Y. Kim, W. Wang, M. Okla, I. Kang, R. Moreau and S. Chung, Suppression of NLRP3 inflammasome by  $\gamma$ -tocotrienol ameliorates type 2 diabetes, *J. Lipid Res.*, 2016, **57**(1), 66–76. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0022227520314024>.
  - 47 F. Fang, Z. Kang and C. Wong, Vitamin E tocotrienols improve insulin sensitivity through activating peroxisome proliferator-activated receptors, *Mol. Nutr. Food Res.*, 2010, **54**(3), 345–352. Available from: <https://onlinelibrary.wiley.com/doi/10.1002/mnfr.200900119>.
  - 48 S. K. Wong, K. Y. Chin, F. H. Suhaimi, F. Ahmad and S. Ima-Nirwana, Vitamin E as a potential interventional treatment for metabolic syndrome: Evidence from animal and human studies, *Front. Pharmacol.*, 2017, **8**(JUL), 1–12.
  - 49 J. A. Goon, N. H. E. Nor Azman, S. M. Abdul Ghani, Z. Hamid, W. Ngah and W. Z. Comparing palm oil tocotrienol rich fraction with  $\alpha$ -tocopherol supplementation on oxidative stress in healthy older adults, *Clin. Nutr. ESPEN*, 2017, **21**, 1–12. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S2405457717302735>.
  - 50 S.-F. Chin, J. Ibahim, S. Makpol, N. A. Abdul Hamid, A. Abdul Latiff, Z. Zakaria, *et al.*, Tocotrienol rich fraction supplementation improved lipid profile and oxidative status in healthy older adults: A randomized controlled study, *Nutr. Metab.*, 2011, **8**(1), 42. Available from: <https://nutritionandmetabolism.biomedcentral.com/articles/10.1186/1743-7075-8-42>.
  - 51 L. L. Chia, I. Jantan, K. H. Chua, K. W. Lam, K. Rullah and M. F. M. Aluwi, Effects of Tocotrienols on Insulin Secretion-Associated Genes Expression of Rat Pancreatic Islets in a Dynamic Culture, *Front. Pharmacol.*, 2016, **7**, 291. Available from: <https://journal.frontiersin.org/Article/10.3389/fphar.2016.00291/abstract>.
  - 52 M. M. Kanchi, M. K. Shanmugam, G. Rane, G. Sethi and A. P. Kumar, Tocotrienols: the unsaturated sidekick shifting new paradigms in vitamin E therapeutics, *Drug Discovery Today*, 2017, **22**(12), 1765–1781. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S135964461730137X>.
  - 53 X. Li, X. Cai, X. Ma, L. Jing, J. Gu, L. Bao, *et al.*, Short-and long-term effects of wholegrain oat intake on weight management and glucolipid metabolism in overweight type-2 diabetics: A randomized control trial, *Nutrients*, 2016, **8**(9), 1–14.
  - 54 U. Tiwari and E. Cummins, Meta-analysis of the effect of  $\beta$ -glucan intake on blood cholesterol and glucose levels, *Nutrition*, 2011, **27**(10), 1008–1016. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0899900710003941>.
  - 55 L. Bao, X. Cai, M. Xu and Y. Li, Effect of oat intake on glycaemic control and insulin sensitivity: A meta-analysis of randomised controlled trials, *Br. J. Nutr.*, 2014, **112**(3), 457–466.
  - 56 E. F. Andrade, R. V. Lobato, T. V. de Araújo, M. G. Zangerônimo, R. V. de Sousa and L. J. Pereira, Effect of beta-glucans in the control of blood glucose levels of diabetic patients: a systematic review, *Nutr. Hosp.*, 2015, **31**(1), 170–177.
  - 57 S. Liatis, P. Tsapogas, E. Chala, C. Dimosthenopoulos, K. Kyriakopoulos, E. Kapantais, *et al.*, The consumption of bread enriched with betaglucan reduces LDL-cholesterol and improves insulin resistance in patients with type2 diabetes, *Diabetes Metab.*, 2009, **35**(2), 115–120. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1262363609000081>.
  - 58 M. Kabir, J.-M. Oppert, H. Vidal, F. Bruzzo, C. Fiquet, P. Wursch, *et al.*, Four-week low-glycemic index breakfast with a modest amount of soluble fibers in type 2 diabetic men, *Metabolism*, 2002, **51**(7), 819–826. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0026049502000021>.
  - 59 C. Cugnet-Anceau, J.-A. Nazare, M. Biorklund, E. Le Coquil, A. Sassolas, M. Sothier, *et al.*, A controlled study of consumption of  $\beta$ -glucan-enriched soups for 2 months by type 2 diabetic free-living subjects, *Br. J. Nutr.*, 2010, **103**(3),



- 422–428. Available from: [https://www.cambridge.org/core/product/identifier/S0007114509991875/type/journal\\_article](https://www.cambridge.org/core/product/identifier/S0007114509991875/type/journal_article).
- 60 F. Li, B. Xu, S. Soltanieh, F. Zanghelini, A. Abu-Zaid and J. Sun, The effects of tocotrienols intake on obesity, blood pressure, inflammation, liver and glucose biomarkers: a meta-analysis of randomized controlled trials, *Crit. Rev. Food Sci. Nutr.*, 2022, **62**(26), 7154–7167. Available from: <https://www.tandfonline.com/doi/full/10.1080/10408398.2021.1911926>.
  - 61 Y. Xue, L. Cui, J. Qi, O. Ojo, X. Du, Y. Liu, *et al.*, The effect of dietary fiber (oat bran) supplement on blood pressure in patients with essential hypertension: A randomized controlled trial, *Nutr. Metab. Cardiovasc. Dis.*, 2021, **31**(8), 2458–2470. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0939475321001836>.
  - 62 A. A. Qureshi, S. A. Sami, W. A. Salser and F. A. Khan, Dose-dependent suppression of serum cholesterol by tocotrienol-rich fraction (TRF25) of rice bran in hypercholesterolemic humans, *Atherosclerosis*, 2002, **161**(1), 199–207. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0021915001006190>.
  - 63 H. Xi, W. Zhou, Y. Niu, R. Zhu, S. Wang, Y. Guo, *et al.*, Effect of Oat Consumption on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials, *J. Acad. Nutr. Diet.*, 2023, **123**(5), 809–823. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S2212267222011960>.
  - 64 S. Ibrügger, M. Kristensen, M. W. Poulsen, M. S. Mikkelsen, J. Ejsing, B. M. Jespersen, *et al.*, Extracted Oat and Barley  $\beta$ -Glucans Do Not Affect Cholesterol Metabolism in Young Healthy Adults, *J. Nutr.*, 2013, **143**(10), 1579–1585. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0022316622013177>.
  - 65 J. Zhang, L. Li, P. Song, C. Wang, Q. Man, L. Meng, *et al.*, Randomized controlled trial of oatmeal consumption versus noodle consumption on blood lipids of urban Chinese adults with hypercholesterolemia, *Nutr. J.*, 2012, **11**(1), 54. Available from: <https://nutritionj.biomedcentral.com/articles/10.1186/1475-2891-11-54>.
  - 66 T. Filippini, M. Malavolti, P. K. Whelton, A. Naska, N. Orsini and M. Vinceti, Blood Pressure Effects of Sodium Reduction, *Circulation*, 2021, **143**(16), 1542–1567. Available from: <https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.050371>.
  - 67 F. Yang, H. Chen, Y. Gao, N. An, X. Li, X. Pan, *et al.*, Gut microbiota-derived short-chain fatty acids and hypertension: Mechanism and treatment, *Biomed. Pharmacother.*, 2020, **130**, 110503. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S075333222030696X>.
  - 68 M. L. Connolly, X. Tzounis, K. M. Tuohy and J. A. Lovegrove, Hypocholesterolemic and Prebiotic Effects of a Whole-Grain Oat-Based Granola Breakfast Cereal in a Cardio-Metabolic “At Risk” Population, *Front. Microbiol.*, 2016, **7**, 1675. Available from: <https://journal.frontiersin.org/article/10.3389/fmicb.2016.01675/full>.
  - 69 P. Khosla, Z. Daud, B. Tubie, M. Sheyman, R. Osia, J. Adams, *et al.*, Vitamin E tocotrienol supplementation improves lipid profiles in chronic hemodialysis patients, *Vasc. Health Risk Manag.*, 2013, **9**, 747–761. Available from: <https://www.dovepress.com/vitamin-e-tocotrienol-supplementation-improves-lipid-profiles-in-chron-peer-reviewed-article-VHRM>.
  - 70 E. C. Heng, S. A. Karsani, M. Abdul Rahman, N. A. Abdul Hamid, Z. Hamid and W. Z. Wan Ngah, Supplementation with tocotrienol-rich fraction alters the plasma levels of Apolipoprotein A-I precursor, Apolipoprotein E precursor, and C-reactive protein precursor from young and old individuals, *Eur. J. Nutr.*, 2013, **52**(7), 1811–1820. Available from: <https://link.springer.com/10.1007/s00394-012-0485-3>.
  - 71 K.-L. Pang and K.-Y. Chin, The Role of Tocotrienol in Protecting Against Metabolic Diseases, *Molecules*, 2019, **24**(5), 923. Available from: <https://www.mdpi.com/1420-3049/24/5/923>.
  - 72 J. Bardhan, R. Chakraborty and U. Raychaudhuri, The 21st Century Form of Vitamin E - Tocotrienol, *Curr. Pharm. Des.*, 2011, **17**(21), 2196–2205. Available from: <https://www.eurekaselect.com/openurl/content.php?genre=article&issn=1381-6128&volume=17&issue=21&page=2196>.
  - 73 A. Li, J. Gao, Y. Li, S. Qi, T. Meng, S. Yu, *et al.*, Efficacy of oats in dyslipidemia: a systematic review and meta-analysis, *Food Funct.*, 2024, **15**(7), 3232–3245. Available from: <https://xlink.rsc.org/?DOI=D3FO04394K>.
  - 74 C.-H. Peng, H.-C. Chang, M.-Y. Yang, C.-N. Huang, S.-J. Wang and C.-J. Wang, Oat attenuate non-alcoholic fatty liver and obesity via inhibiting lipogenesis in high fat-fed rat, *J. Funct. Foods*, 2013, **5**(1), 53–61. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1756464612001156>.
  - 75 C.-L. Shen, S. Wang, S. Yang, M. D. Tomison, M. Abbasi, L. Hao, *et al.*, A 12-week evaluation of annatto tocotrienol supplementation for postmenopausal women: safety, quality of life, body composition, physical activity, and nutrient intake, *BMC Complement. Altern. Med.*, 2018, **18**(1), 198. Available from: <https://bmccomplementalmed.biomedcentral.com/articles/10.1186/s12906-018-2263-0>.
  - 76 E. Magosso, M. Ansari, Y. Gopalan, I. Shuaib, J. Wong, N. A. Khan, *et al.*, Tocotrienols for normalisation of hepatic echogenic response in nonalcoholic fatty liver: A randomised placebo-controlled clinical trial, *Nutr. J.*, 2013, **12**(1), 166.
  - 77 L. Leão, L. A. Aquino, J. F. Dias and R. J. Koifman, Addition of oat bran reduces HDL-C and does not potentialize effect of a low-calorie diet on remission of metabolic syndrome: a pragmatic, randomized, controlled, open-label nutritional trial, *Nutrition*, 2019, **65**, 126–130. Available from: <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01939857/full>.
  - 78 G. C. Burdeos, K. Nakagawa, F. Kimura and T. Miyazawa, Tocotrienol Attenuates Triglyceride Accumulation in HepG2 Cells and F344 Rats, *Lipids*, 2012, **47**(5), 471–481. Available from: <https://aocs.onlinelibrary.wiley.com/doi/10.1007/s11745-012-3659-0>.
  - 79 L. Zhao, I. Kang, X. Fang, W. Wang, M. A. Lee, R. R. Hollins, *et al.*, Gamma-tocotrienol attenuates high-fat diet-induced obesity and insulin resistance by inhibiting





- adipose inflammation and M1 macrophage recruitment, *Int. J. Obes.*, 2015, **39**(3), 438–446. Available from: <https://www.nature.com/articles/ijo2014124>.
- 80 W.-Y. Wong, L. C. Ward, C. W. Fong, W. N. Yap and L. Brown, Anti-inflammatory  $\gamma$ - and  $\delta$ -tocotrienols improve cardiovascular, liver and metabolic function in diet-induced obese rats, *Eur. J. Nutr.*, 2017, **56**(1), 133–150. Available from: <https://link.springer.com/10.1007/s00394-015-1064-1>.
  - 81 K. L. Pang and K. Y. Chin, The role of tocotrienol in protecting against metabolic diseases, *Molecules*, 2019, **24**(5), 923.
  - 82 Y.-X. Wang, PPARs: diverse regulators in energy metabolism and metabolic diseases, *Cell Res.*, 2010, **20**(2), 124–137. Available from: <https://www.nature.com/articles/cr201013>.
  - 83 H. Uto-Kondo, R. Ohmori, C. Kiyose, Y. Kishimoto, H. Saito, O. Igarashi, *et al.*, Tocotrienol Suppresses Adipocyte Differentiation and Akt Phosphorylation in 3T3-L1 Preadipocytes, *J. Nutr.*, 2009, **139**(1), 51–57. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0022316622065105>.
  - 84 T. Kawada, Y. Kamei, A. Fujita, Y. Hida, N. Takahashi, E. Sugimoto, *et al.*, Carotenoids and retinoids as suppressors on adipocyte differentiation via nuclear receptors, *BioFactors*, 2000, **13**(1–4), 103–109. Available from: <https://iubmb.onlinelibrary.wiley.com/doi/10.1002/biof.5520130117>.
  - 85 M. Cesari, M. Pahor, B. Bartali, A. Cherubini, B. W. J. H. Penninx, G. R. Williams, *et al.*, Antioxidants and physical performance in elderly persons: The Invecchiare in Chianti (InCHIANTI) study, *Am. J. Clin. Nutr.*, 2004, **79**(2), 289–294.
  - 86 J. M. Sacheck, P. E. Milbury, J. G. Cannon, R. Roubenoff and J. B. Blumberg, Effect of vitamin E and eccentric exercise on selected biomarkers of oxidative stress in young and elderly men, *Free Radicals Biol. Med.*, 2003, **34**(12), 1575–1588. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0891584903001874>.
  - 87 M. Meydani, W. J. Evans, G. Handelman, L. Biddle, R. A. Fielding, S. N. Meydani, *et al.*, Protective effect of vitamin E on exercise-induced oxidative damage in young and older adults, *Am. J. Physiol.: Regul., Integr. Comp. Physiol.*, 1993, **264**(5), R992–R998. Available from: <https://www.physiology.org/doi/10.1152/ajpregu.1993.264.5.R992>.
  - 88 S. C. Khor, N. Abdul Karim, W. Z. Wan Ngah, Y. A. Mohd Yusof and S. Makpol, Vitamin E in Sarcopenia: Current Evidences on Its Role in Prevention and Treatment, *Oxid. Med. Cell. Longevity*, 2014, **2014**, 1–16. Available from: <https://www.hindawi.com/journals/omcl/2014/914853/>.
  - 89 J. Y. Lee and S. Lee, Dietary Patterns Related to Appendicular Skeletal Muscle Mass: The Korea National Health and Nutrition Examination Survey 2008–2011, *J. Am. Coll. Nutr.*, 2019, **38**(4), 358–363. Available from: <https://www.tandfonline.com/doi/full/10.1080/07315724.2018.1523759>.
  - 90 C. Xu, J. Lv, Y. M. Lo, S. W. Cui, X. Hu and M. Fan, Effects of oat  $\beta$ -glucan on endurance exercise and its anti-fatigue properties in trained rats, *Carbohydr. Polym.*, 2013, **92**(2), 1159–1165. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0144861712010429>.
  - 91 J. Pattanaphesaj and M. Thavorncharoensap, Measurement properties of the EQ-5D-5L compared to EQ-5D-3L in the Thai diabetes patients, *Health Qual. Life Outcomes*, 2015, **13**(1), 14. Available from: <https://hqlo.biomedcentral.com/articles/10.1186/s12955-014-0203-3>.
  - 92 E. y. Wong, R. H. Xu and A. I. Cheung, Measurement of health-related quality of life in patients with diabetes mellitus using EQ-5D-5L in Hong Kong, China, *Qual. Life Res.*, 2020, **29**(7), 1913–1921. Available from: <https://link.springer.com/10.1007/s11136-020-02462-0>.
  - 93 Y. Wang, N.-C. Tan, E.-G. Tay, J. Thumboo and N. Luo, Cross-cultural measurement equivalence of the 5-level EQ-5D (EQ-5D-5L) in patients with type 2 diabetes mellitus in Singapore, *Health Qual. Life Outcomes*, 2015, **13**(1), 103. Available from: <https://hqlo.biomedcentral.com/articles/10.1186/s12955-015-0297-2>.
  - 94 A. G. Tsai, T. A. Wadden, D. B. Sarwer, R. I. Berkowitz, L. G. Womble, L. A. Hesson, *et al.*, Metabolic Syndrome and Health-related Quality of Life in Obese Individuals Seeking Weight Reduction, *Obesity*, 2008, **16**(1), 59–63. Available from: <https://onlinelibrary.wiley.com/doi/10.1038/oby.2007.8>.
  - 95 Y.-J. Lee, S. Y. Woo, J. H. Ahn, S. Cho and S. R. Kim, Health-Related Quality of Life in Adults with Metabolic Syndrome: The Korea National Health and Nutrition Examination Survey, 2007–2008, *Ann. Nutr. Metab.*, 2012, **61**(4), 275–280. Available from: <https://www.karger.com/Article/FullText/341494>.
  - 96 T. Zhou, H. Guan, L. Wang, Y. Zhang, M. Rui and A. Ma, Health-Related Quality of Life in Patients With Different Diseases Measured With the EQ-5D-5L: A Systematic Review, *Front. Public Health*, 2021, **9**, 675523. Available from: <https://www.frontiersin.org/articles/10.3389/fpubh.2021.675523/full>.

