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Validation of the German version of the Mediterranean Diet Adherence Screener (MEDAS) questionnaire

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Abstract

Background: Health benefits of the Mediterranean Diet (MD) have been shown in different at-risk populations. A German translation of the Mediterranean Diet Adherence Screener (MEDAS) from the PREvención con Dieta MEDiterránea (PREDIMED) consortium was used in the LIBRE study, investigating effects of lifestyle-intervention on women with BRCA1/2 mutations. The purpose of the present study is to validate the MEDAS German version.

Methods: LIBRE is a multicentre (three university hospitals during this pilot phase), unblinded, randomized, controlled clinical trial. Women with a BRCA1/2 mutation of age 18 or over who provided written consent were eligible for the trial. As part of the assessment, all were given a full-length Food Frequency Questionnaire (FFQ) and MEDAS at baseline and after 3 months. Data derived from FFQ was compared to MEDAS in order to evaluate agreement or concordance between the two questionnaires. Additionally, the association of dietary intake biomarkers in the blood (β -carotene, omega-3, omega-6 and omega-9 fatty acids and high-sensitivity C-reactive protein (hsCRP)) with some MEDAS items was analyzed using t-Tests and a multivariate regression.

Results: The participants of the LIBRE pilot study were 68 in total (33 Intervention, 35 Control). Only participants who completed both questionnaires were included in this analysis (baseline: 66, month three: 54). The concordance between these two questionnaires varied between the items (Intraclass correlation coefficient of 0.91 for pulses at the highest and -0.33 for sugar-sweetened drinks). Mean MEDAS scores (sum of all items) were 9% higher than their FFQ counter-parts at baseline and 15% after 3 months. Higher fish consumption (at least 3 portions) was associated with lower omega-6 fatty acid levels ($p = 0.026$) and higher omega-3 fatty acid levels ($p = 0.037$), both results being statistically significant.

Conclusions: We conclude that the German MEDAS in its current version could be a useful tool in clinical trials and in practice to assess adherence to MD.

Trial registration: ClinicalTrials.gov, registered on March 12, 2014, identifier: NCT02087592. World Health Organization Trial Registration, registered on 3 August 2015, identifier: NCT02087592.

Keywords: Mediterranean diet adherence, Hereditary breast cancer, BRCA1/2, Food frequency, Validation

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Background

The MD has been tested for its health benefits in different at-risk populations with favourable results. For instance, randomized controlled intervention studies revealed that MD is effective in the primary prevention of cardiovascular diseases [1, 2], in lowering hypertension and atherogenic lipoproteins [3, 4] and in improving diabetes [5]. More recently, studies in the older population showed an association between MD and improved cognitive function [6]. Epidemiological studies from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort suggested further that MD might protect against cancer, especially gastric cancer [7], colorectal cancer [8] and bladder cancer [9].

Such trials raised the need for a useful tool to assess MD adherence in study populations. The PREDIMED consortium established a 14-point MEDAS questionnaire, which was validated by administering the established FFQ [10] and MEDAS to 7146 participants from the PREDIMED study. The authors found that the average MEDAS score estimate was 105% of the FFQ PREDIMED score estimate, and thus is a valid instrument for rapid estimation of adherence to the MD [11]. Moreover, the PREDIMED investigators could show that MEDAS is able to capture a strong monotonic inverse association between adherence to MD and obesity indices in a population of adults with a high cardiovascular risk [12].

In Germany, a multicentre trial, the 'Lifestyle intervention in BRCA 1/2-mutation carriers' (LIBRE) was launched to investigate the effect of a defined lifestyle intervention on breast cancer incidence in women at high genetic risk for this type of cancer [13]. Up to 60% of women with BRCA mutations develop breast or ovarian cancer [14], but not all of them, suggesting that environmental cofactors play a role. Indeed, some studies suggested that physical activity and dietetic intervention help prevent cancer, including breast cancer [15, 16]. To test the hypothesis of whether these controllable environmental factors further modulate cancer risk, the LIBRE trial conducts an intervention with clearly defined sport and nutrition components. The nutritional component of the intervention was based on the MD. The German translation of MEDAS was used as an instrument to assess adherence. The purpose of the present study was to validate the German version of MEDAS.

Methods

Study population

The LIBRE study is divided into two parts: firstly, a feasibility study to prove the practicability of the lifestyle intervention and consequently, the presently recruiting main trial with the aim of attaining 600 study participants to demonstrate the effects of the lifestyle intervention on the breast cancer incidence in women with BRCA1 or BRCA2

genetic mutations. 68 women, who were all participants of the LIBRE feasibility study, formed the study population for these analyses. The details of the trial have been published elsewhere [13]. The study population (adult women between 18 and 75 years) was recruited from February 2014 to July 2014 in selected consultation centres of the German Consortium of Hereditary Breast and Ovarian Cancer in Kiel, Cologne and Munich. All participants signed an informed written consent. The trial was approved by the responsible ethical committees.

Study participants were randomized into two groups with a ratio of 1:1, stratified by participating centre and previous breast cancer. The intervention group (IG) ($n = 35$) received a detailed lifestyle intervention over 12 months, and the control group (CG) ($n = 33$) received no intervention, but standard recommendations for a healthier lifestyle. The lifestyle IG received a supervised physical exercise training program and nutritional education based on the MD. In the first 3 months, the nutritional education took place every fortnight, thereafter at monthly intervals. The CG received minimal nutritional education based on the recommendations of the German Society of Nutrition (DGE - <https://www.dge.de/en/>) "Usual Care in Germany" and some general advice for increasing activity in everyday life at the beginning of the study (one session). All participants were asked to fill out both a full-length FFQ and MEDAS at study start (baseline) and 3 months later. We chose both time points to prove whether MEDAS is specific enough by measuring MD-typical changes during the intervention. Only data collected within this period were used for the purposes of the current study. Solely participants who had completed both questionnaires were included in the analysis. These were in total 66 participants at baseline (34 in the IG and 32 in the CG) and 54 at month three (27 in the IG and 27 in the CG).

We used the guidelines from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) to guide our translation process [17]. MEDAS from the English PREDIMED-publication [11] was translated into German and reviewed by two native speakers in German. It was then translated back into English by a native speaker. Following this, the final version was read and approved in a small group of the study team.

Dietary assessment

MEDAS is a 14-item screener, which consists of 12 questions on food consumption frequency and 2 questions on food intake habits characteristic of the MD (Table 1). Each question was scored with a 0 or 1. One point was given for using olive oil as the principal source of fat for cooking and one for preferring white meat over red meat, and one for consuming each of the following:

Table 1 MEDAS questions and transfer of food intake data from FFQ into its food groups

MEDAS question	data recorded by FFQ
1. Do you use olive oil as the principal source of fat for cooking?	1 point given: use of olive oil for the preparation of at least 2 of the following groceries: salad, vegetable, meat/fish (FFQ Question: Pages 14 and 19)
2. How much olive oil do you consume per day (including that used in frying, salads, meals eaten away from home, etc.)?	1 point given: based on FFQ calculation, if >48 g vegetable oil
3. How many servings of vegetables do you consume per day?	1 point given: based on FFQ calculation, if ≥ 2 portions of vegetables per day (including salad, olives, mushrooms)
4. How many pieces of fruit (including fresh-squeezed juice) do you consume per day?	1 point given: based on FFQ calculation, if ≥ 3 portions of fruit (including mixed fruit, mixed stewed fruit and fruit juices)
5. How many servings of red meat, hamburger, or sausages do you consume per day?	1 point given: based on FFQ calculation, if <100 g meat (beef, veal, pork, lamb) and processed meat products
6. How many servings (12 g) of butter, margarine, or cream do you consume per day?	1 point given: based on FFQ calculation, if <1 portion butter, margarine and cream
7. How many carbonated and/or sugar-sweetened beverages do you consume per day?	1 point given: based on FFQ calculation, sugar-sweetened beverages <1 portion per day (including lemonade and colas)
8. Do you drink wine? How much do you consume per week?	1 point given: based on FFQ calculation, if ≥ 7 portions wine (red and white)
9. How many servings of pulses do you consume per week?	1 point given: ≥ 3 portions pulses per week (page 14)
10. How many servings of fish/seafood do you consume per week?	1 point given: based on FFQ calculation, if ≥ 3 portions fish, fish products and seafood per week
11. How many times do you consume commercial (not homemade) pastry such as cookies or cake per week?	1 point given: based on FFQ calculation, if <3 portions cakes, chocolate, cookies, sweets with and without chocolate per week
12. How many times do you consume nuts per week?	1 point given: based on FFQ calculation, if ≥ 3 portions nuts and seeds per week (page 11)
13. Do you prefer to eat chicken, turkey or rabbit instead of beef, pork, hamburgers, or sausages?	1 point given: based on FFQ calculation, if g white meat (poultry, chicken, rabbit) > g red meat (beef, veal, pork, lamb, processed meat products)
14. How many times per week do you consume boiled vegetables, pasta, rice, or other dishes with a sauce of tomato, garlic, onion, or leeks sautéed in olive oil?	1 point given: > 1–2 times a week tomato sauce (page 21)

- 4 or more tablespoons (1 tablespoon = 13.5 g) of olive oil/d (including that used in frying, salads, meals eaten away from home, etc.);
- 2 or more servings of vegetables/d;
- 3 or more pieces of fruit/d;
- fewer than 1 serving of red meat or sausages/d;
- fewer than 1 serving of animal fat/d;
- fewer than 1 cup (1 cup = 100 mL) of sugar-sweetened beverages/d;
- 7 or more servings of red wine/wk.;
- 3 or more servings of pulses/wk.;
- 3 or more servings of fish/wk.;
- fewer than 3 commercial pastries/wk.;
- 3 or more servings of nuts/wk.; or
- 2 or more servings/wk. of a dish with a traditional sauce of tomatoes, garlic, onion, or leeks sautéed in olive oil.

If the condition was not met, 0 points were recorded for the category. The MEDAS score (sum of above items) ranged from 0 to 14 points [11].

All participants were also asked to complete a 148-item semi-quantitative FFQ. The German version had been validated by the German EPIC investigators [18–21]. For each item it questions the average serving size, described by photos, and the food frequency during the previous 12 months. Furthermore, it contains questions on cooking oil, frequency of the use of gravy, the fat content of dairy products, the use of sugar and milk in coffee and tea, and the seasonal consumption of fruit and vegetables. The documentation of the questionnaire was done via *the study-management-system for Epidemiology and Public Health*, which was developed and supervised by the Department of Epidemiology of the German Institute of Human Nutrition Potsdam-Rehbruecke.

Food intake data recorded by FFQ was grouped into the food-based dietary components of MEDAS (Table 1). We validated the dietary assessment data retrieved from MEDAS by comparing it with the data gathered from the validated FFQ and confirmed this by associating with the results from the blood tests.

Measurement of dietary intake biomarkers in the blood

To confirm whether MEDAS' tendency towards the MD is consistent, we selected specific biomarkers in the blood which are described in the literature to be associated with consumption of certain MD food components [1, 22, 23].

Blood samples were taken at the same time points as the completion of both questionnaires (baseline and after 3 month). Following 30 to 60 min of incubation the serum was centrifuged at 3000*g for 10 min in the consultation centres and was overnight delivered chilled together with the EDTA (ethylene diamine tetraacetic acid) blood samples to the central laboratory at the University of Hohenheim.

A part of the serum was passed directly to an external laboratory (Medizinisches Labor Bremen, Bremen, Germany) to measure β-carotene by high performance liquid chromatography (HPLC). The rest of the serum aliquots were stored at -80 °C in Hohenheim until the measurement of hsCRP using a sandwich Enzyme Immuno Assay (K 9710S, Immundiagnostik AG, Bensheim, Germany) was done. The erythrocyte membrane was isolated from the EDTA blood and also stored at -80 °C in Hohenheim until the fatty acid profile (omega-6-, omega-3- and omega-9-fatty acids) was analyzed after acid esterification using gas chromatography/mass spectrometry by the Institute of Food Chemistry of the University of Hohenheim [24, 25].

Statistical analysis

Patient characteristics were analyzed descriptively, split by study arm. For age and Body Mass Index (BMI), a t-Test was used to determine whether the two groups were statistically different. For all other characteristics, coded as binary items, a Chi² test was used.

We then determined the concordance between the answers to the MEDAS questionnaire compared to the answers for corresponding questions in the FFQ questionnaire both at Baseline and at 3 months. First, the absolute agreement in percentage was calculated, which was further investigated using Cohen's kappa (κ) and the intraclass correlation coefficient (ICC). The relative agreement between the corresponding items was examined using the Pearson product-moment correlation.

The agreement between the sum from the MEDAS questionnaire and the equivalent FFQ questions was examined using a Bland-Altman analysis. The mean of the two values was plotted on the x-axis and the difference on the y-axis, in order to determine possible bias. The 95% limits of agreement lines, defined as the mean difference ± 1.96 times the standard deviation of the differences, were also plotted. A linear regression was then carried out with the difference as the dependent value, whose line was added to the plot with its corresponding formula and p-value.

In a further step, we validated whether the MEDAS questionnaire can specifically determine adherence to a MD, the association of blood values for β-carotene, the fatty acids omega-3, omega-6 and omega-9 and hsCRP, and MEDAS items (β-carotene associated with the MEDAS item regarding vegetables and fruits; hsCRP, omega-3 fatty acids, omega-6 fatty acids and omega-9 fatty acids associated with the MEDAS item regarding olive oil; omega-3 fatty acids and omega-6 fatty acids associated with the MEDAS item regarding red meat, fish and nuts). We first applied a t-Test for independent groups (control or intervention) for each of the food items and each of the dietary biomarker values, carried out separately for each of the two time points. Following this, we carried out a multivariate linear regression on the associations described above, where we also adjusted for the study arm.

The statistical analysis was done using R (program for statistical computing) in the R Studio environment Version 0.99.902.

Results

Patient characteristics

Patient characteristics at baseline are outlined in Table 2. The IG comprised 35 women at this point in time, while the CG comprised 32. Considering attributes such as BMI, age and history of breast cancer, these groups did not differ statistically significantly from one another. Both groups included a number of smokers (11% in the IG and 9% in the CG). A vegetarian diet was also followed by a group of the study participants (6% in the IG and 13% in the CG).

Item by item agreement

The absolute and relative agreements between the FFQ and the MEDAS questionnaires were calculated at baseline and at 3 months for the whole sample (Table 3). This concordance at Baseline was highest for questions 1: olive oil as principal source of fat (Pearson's product-moment correlation 0.70, κ 0.70 and an ICC of 0.68), and 12: nuts (Pearson's product-moment correlation 0.72, κ 0.70 and an ICC of 0.68). After 3 months the highest concordance was obtained for questions 9: pulses (Pearson's product-moment correlation 0.86, κ

Table 2 Study patient characteristics at baseline (n = 67)

	Intervention group (MD) n = 34	Control group N = 32
Age [years] ^a	42 (27–72)	42 (24–68)
BMI [kg per m ²] ^a	23 (18–45)	23 (18–43)
History of breast cancer ^b	24 (71%)	21 (66%)
Smoker ^b	4 (11%)	3 (9%)
Vegetarian ^b	2 (6%)	4 (13%)

^amedian (range)

^bnumbers (percent)

Table 3 Agreement between MEDAS and FFQ (German)

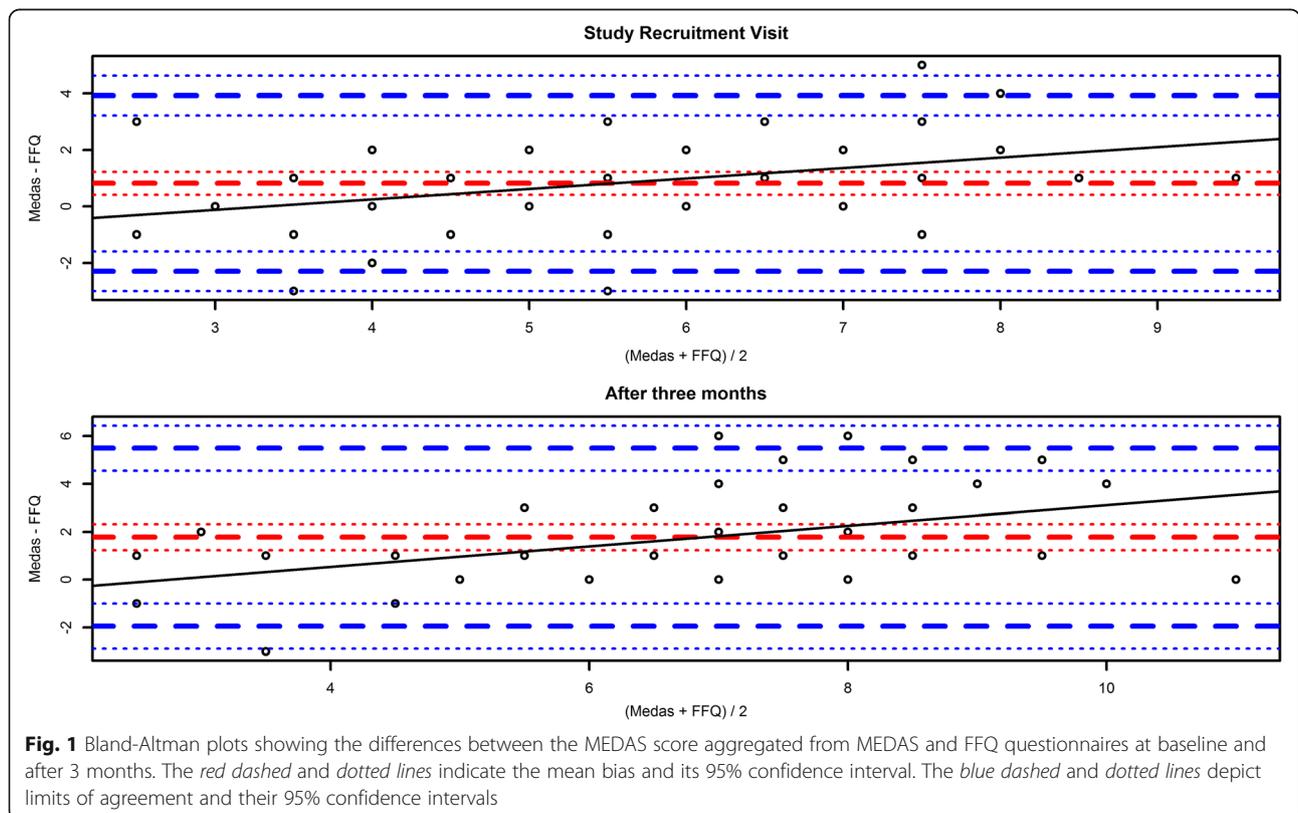
Question	Baseline (n = 66)				3 months (n = 54)			
	r	AA	κ	ICC	r	AA	κ	ICC
1	0.70	0.87	0.70 (0.51 to 0.89)	0.68 (0.07 to 1.3)	0.51	0.87	0.51 (0.22 to 0.81)	0.55 (-0.19 to 1.28)
2	0.29	0.86	0.23 (-0.07 to 0.53)	0.21 (-0.35 to 0.76)	-0.09	0.70	-0.034 (-0.1 to 0.03)	-0.03 (-0.08 to 0.02)
3	0.30	0.63	0.28 (0.06 to 0.49)	0.14 (-0.26 to 0.54)	0.25	0.62	0.19(-0.02 to 0.4)	0.15 (-0.36 to 0.66)
4	0.42	0.70	0.36 (0.15 to 0.56)	0.28 (-0.33 to 0.88)	0.08	0.25	0.087 (-0.16 to 0.31)	-0.03 (-0.06 to 0.01)
5	0.58	0.81	0.50 (0.28 to 0.72)	0.52 (-0.20 to 1.24)	0.40	0.87	0.39 (0.03 to 0.75)	0.04 (-0.35 to 1.14)
6	0.45	0.73	0.45 (0.22 to 0.67)	0.32 (-0.33 to 0.97)	0.23	0.61	0.22 (-0.03 to 0.48)	0.06 (-0.20 to 0.33)
7	-0.04	0.91	-0.03 (-0.07 to 0.02)	-0.11 (-0.14 to -0.08)	n/a	0.96	n/a	-0.33 (-0.38 to -0.28)
8	0.35	0.83	0.28 (-0.001 to 0.57)	0.51 (-0.28 to 1.30)	0.24	0.91	0.21 (-0.19 to 0.6)	0.37 (-0.57 to 1.31)
9	n/a	0.92	n/a	n/a	0.86	0.96	0.85 (0.66 to 1.1)	0.91 (0.68 to 1.14)
10	0.25	0.84	0.21 (-0.18 to 0.61)	0.22 (-0.42 to 0.87)	0.28	0.74	0.21 (-0.04 to 0.45)	0.13 (-0.28 to 0.55)
11	0.44	0.77	0.37 (0.14 to 0.6)	0.33 (-0.33 to 0.99)	0.64	0.83	0.61 (0.39 to 0.83)	0.58 (-0.13 to 1.28)
12	0.72	0.86	0.70 (0.52 to 0.87)	0.68 (0.05 to 1.30)	0.78	0.89	0.77 (0.61 to 0.94)	0.76 (0.23 to 1.28)
13	0.18	0.43	0.06 (-0.01 to 0.13)	0.03 (-0.14 to 0.20)	0.13	0.27	0.03 (-0.01 to 0.08)	0.01 (-0.15 to 0.13)
14	0.39	0.69	0.38 (0.16 to 0.6)	0.25 (-0.33 to 0.83)	0.17	0.60	0.17 (-0.01 to 0.43)	0.02 (-0.14 to 0.18)

AA = absolute agreement, r = Pearson’s product–moment correlation, κ = Cohen’s Kappa with the confidence intervals in brackets, ICC = Intraclass Correlation Coefficient with the confidence intervals in brackets

0.85 and an ICC of 0.91), and 12: nuts (Pearson’s product–moment correlation 0.78, κ 0.77 and an ICC of 0.76). Questions 7: sugar-sweetened beverages at Baseline and 2: daily olive oil had the lowest concordances with negative values.

MEDAS total score agreement

The MEDAS score was analyzed using a Bland-Altman plot (Fig. 1). The mean MEDAS scores were 15% higher than the FFQ score at baseline and 23% higher after 3 months, with the median MEDAS score being higher



than the FFQ equivalent by 1 point at baseline and 2 points after 3 months. This corresponds to a mean difference of 1.27 at baseline and 2.12 after 3 months, which defines the bias towards higher score sums being obtained by the MEDAS questionnaire. Linear regression analysis revealed a significant increase of the bias with increasing score values ($p < 0.001$ for baseline, $p < 0.001$ after 3 months).

Measurement of dietary intake biomarkers in the blood

The possible association between laboratory measurements and intake of particular food groups was first analyzed on a per item basis (Table 4). After the 3-month MD intervention some of these associations showed a statistical significance or near-significance. Consumption of at least 3 portions of fish per week was associated with lower omega-6 fatty acid levels ($p = 0.035$) and higher omega-3 fatty acid levels ($p = 0.053$). Consumption of at least 3 portions of fruit per day was associated with higher levels of β -carotene ($p = 0.056$). Consumption of at least 2 portions of vegetables per day was associated with higher levels of β -carotene ($p = 0.004$). We have depicted these associations in Fig. 2.

We also examined the same associations in a multivariate model, as reported in Table 5. Consumption of at least three portions of fish per week showed increased

levels of omega-3 ($p = 0.037$) and decreased levels of omega-6 fatty acid ($p = 0.026$) in the blood, both of which were statistically significant.

Discussion

MEDAS was developed for the Spanish PREDIMED study to expediently determine adherence to the MD and allow an immediate feedback to the patient. This short screener is a validated tool for the rapid assessment of adherence to the MD [11], which is why it was decided to use a German-translation of this questionnaire in the LIBRE study. However, the original MEDAS was not in German. To validate the German translation of this questionnaire, we used the validated German full-length FFQ as reference.

In general agreement between FFQ and MEDAS questionnaires was of a fair or better level (0.4 and larger values for agreement coefficients) for about half of the MEDAS questions [22]. These differences are likely due to the way FFQ is structured and to the fact that it is differently analyzed. FFQ measures the food frequency of a selected list of German foods with standardized portion sizes for the previous 12 months. These answers are then used to calculate intake for food groups while MEDAS directly asks for the habits and consumption frequency of specific amounts of specific Mediterranean

Table 4 MEDAS food groups association with dietary biomarkers in the blood

MEDAS food group association with dietary biomarker(s)	Baseline (n = 66)			At 3 months(n = 54)		
	Mean for group with 0 point (n)	Mean for group with 1 point (n)	p-value	Mean for group with 0 point (n)	Mean for group with 1 point (n)	p-value*
vegetables with						
β -carotene [$\mu\text{g/l}$]	859.7 (26)	889.3 (39)	0.868	487.8 (9)	918.9 ¹ (45)	0.004
fruit with						
β -carotene [$\mu\text{g/l}$]	786.6 (36)	1009.5 ¹ (29)	0.183	689.5 (25)	984.18 ¹ (29)	0.056
how much olive oil with						
hsCRP [mg/l]	0.6 (54)	0.5 ¹ (11)	0.337	0.7 (39)	0.5 ¹ (15)	0.218
omega 3 [%]	14.0 (54)	13.7 (11)	0.763	13.2 (39)	13.8 ¹ (15)	0.513
omega 6 [%]	27.5 (54)	27.3 (11)	0.831	25.0 (39)	25.0 ¹ (15)	0.983
omega 9 [%]	14.08 (54)	13.77 (11)	0.185	15.4 (39)	15.16 (15)	0.362
red meat with						
omega 3 [%]	14.2 (21)	13.8 (44)	0.665	12.1 (8)	13.3 (45)	0.202
omega 6 [%]	27.5 (21)	27.4 (44)	0.908	25.0 (8)	25.2 (45)	0.849
fish with						
omega 3 [%]	14.1 (59)	12.6 (6)	0.280	12.6 (38)	15.1 ¹ (16)	0.053
omega 6 [%]	27.4 (59)	27.9 (6)	0.629	25.6 (38)	23.4 ¹ (16)	0.035
nuts with						
omega 3 [%]	13.5 (38)	14.5 (27)	0.230	13.8 (23)	13.2 (30)	0.559
omega 6 [%]	27.8 (38)	26.9 (27)	0.811	24.4 (23)	25.4 (30)	0.361

*based on the t-test
Only significant P values are bold

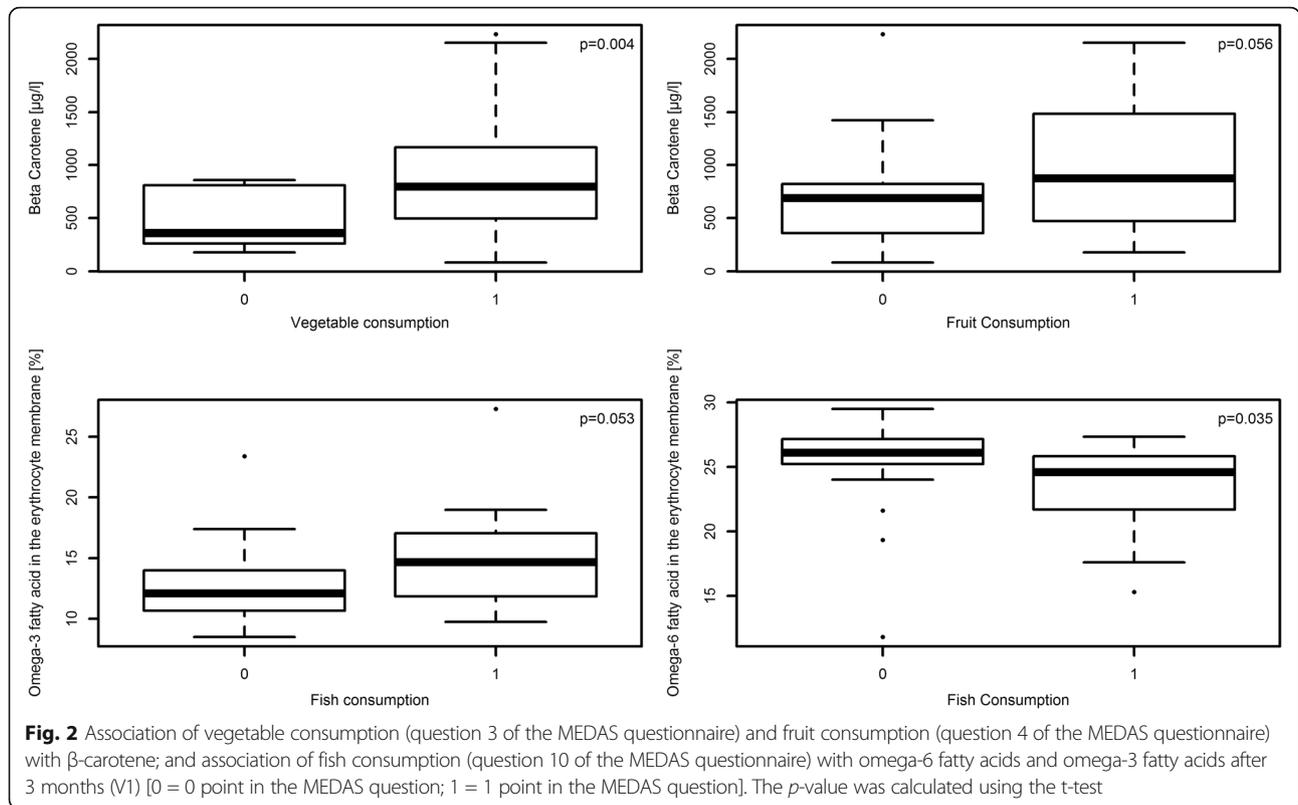


Table 5 Dietary blood biomarkers association with MEDAS food groups, assessed using multivariate regression

Dietary biomarker association with MEDAS food group	Baseline		At 3 months	
	Estimate	p -Value	Estimate	p -Value*
β-Carotene with				
Fresh vegetables	-22	0.197	446	0.104
Fruits	237	0.287	366	0.147
omega 3 with				
Amount of olive oil	-0.99	0.415	1.1	0.230
Red meat	-0.99	0.282	2.2	0.099
Fish	-2.1	0.133	2.1	0.037
Nuts	1.5	0.094	-1.2	0.225
omega 6 with				
Amount of olive oil	0.269	0.775	-0.4	0.702
Red meat	0.243	0.734	-1.3	0.360
Fish	0.834	0.433	-2.4	0.026
Nuts	-0.96	0.162	1.5	0.147
omega 9 with				
Amount of olive oil	-0.095	0.114	-0.054	0.542
HsCRP with				
Amount of olive oil	-0.234	0.402	-0.3	0.161

*adjusted for the study arm
Only significant P values are bold

foods during the previous week. In short, the FFQ measures specific details whereas the MEDAS is measuring for components of an overall dietary pattern. For the conversion of food intake data from FFQ into MEDAS food groups only aggregated FFQ data can be used in most cases. For instance, question 3 on vegetables and question 4 on fruits each comprised several questions from FFQ. A further example is that FFQ provides, 3no information on how many times boiled vegetables, pasta, rice, or other dishes with a sauce of tomato, garlic, onion, or leeks sautéed in olive oil are consumed. It asks only about the consumption of tomato sauce, but no further details (e.g. way of cooking or ingredients). Only question 9 (pulses) which has a high concordance is based on a direct answer of FFQ. Additionally, in this study FFQ was completed again within after an interval of just 3 months, which means that the answers for the two time points for FFQ in our analysis overlap for a period of time.

The Bland-Altman analysis showed that the MEDAS score yields higher values for the sum of all items than FFQ with respect to MD. This confirms the results of Schröder et al., who report that the average MEDAS Mediterranean diet score estimate was 105% of the FFQ PREDIMED score estimate [11]. The larger difference between the two score sets after 3 months can be a result of the MD-based intervention in the IG. The MEDAS

questionnaire was specifically developed to detect the adherence of an individual's diet to the principles of the MD. Therefore, MEDAS is more sensitive for MD items than FFQ, resulting in higher scores in individuals abiding by the MD. The FFQ questions, however, assesses the general food intake and does not focus particularly on the consumption of Mediterranean food. Two points can be considered relevant for detecting an adequate implementation of MD in life.

To confirm if the MEDAS' tendency towards the MD is consistent, we analyzed the association between certain MD food items and selected dietary intake biomarkers in the blood thought to be associated with these food items. The traditional MD is characterized by a high intake of olive oil, fruit, nuts, vegetables, and cereals; a moderate intake of fish and poultry; and a low intake of dairy products, red meat, processed meats, and sweets; while wine is consumed moderately and only together with meals [1, 23]. In the literature, it is described that a high consumption of fruits and vegetables is associated with higher β -carotene blood levels [26]. Kitamura et al. have previously positively correlated frequency of vegetables and fruit intake with β -carotene, among other things [26]. In our study, subjects who consumed at least two portions of vegetables per day according to the MEDAS questionnaire had higher β -carotene blood levels than those who consumed fewer than two portions at both time points. Those who consumed at least three portions of fruit per day according to the MEDAS questionnaire also had higher β -carotene levels in their blood than those who consumed fewer than three portions. This data supports that the MEDAS results reflect the reported intake of particular nutrients characteristic of a MD pattern.

The MD is rich in poly- and mono-unsaturated fatty acids due to the high consumption of olive oil, fish and nuts [27]. The amount of saturated fatty acids in the MD is lower than in the *Western-style* diet, because red meat and processed meat products play a minor part in the Mediterranean nutrition. The *Western-style* diet is characterized by its highly processed and refined foods and high contents of sugars, salt and fat and protein from red meat [28]. Olive oil is characterized by a high content of mono-unsaturated fatty acids. Oleic acid (C18:1, n-9) is the main component of olive oil [27]. Therefore, we hypothesized that a high consumption of olive oil, fish and nuts and low red meat intake are associated with changes in the fatty acid profile measured in erythrocyte membrane. Barcelo et al. described elevated values of omega-3-fatty acids and low values of omega-6-fatty acids following high olive oil consumption, while the omega-9-fatty acid amount remained unchanged [29]. Our data demonstrated that, more than four tablespoons of olive oil per day were associated with a tendency to higher serum levels of all unsaturated fatty

acids (omega-6, -3 and -9) compared with the values measured in subjects who consumed less olive oil. Takumen et al. described an association between high fish consumption and a change in the omega-6 and -3-fatty acids profile. The amount of omega-6-fatty acids decreased while that of omega-3-fatty acids increased [30]. At least three portions of fish and seafood per week were statistically significantly associated with lower omega-6-fatty acids values (24% compared to 26.3%, $p = 0.016$) and higher omega-3-fatty acids values. While high meat consumption is associated with higher omega-6-fatty acids values [30], such tendencies could also be seen in this study.

Barceló et al. [29] also reported an association between hsCRP values and olive oil consumption. According to their data, a MD enriched with olive oil (1 litre per week) resulted in a reduction of the plasma hsCRP concentration. Such tendencies could also be seen in this study. Individuals who consume more than four tablespoons of olive oil per day had lower values of hsCRP than individuals who consume less olive oil. The described associations between certain food items and blood values indicate that the MEDAS score indeed reflects a MD. Within this context, MEDAS provides reasonable estimates to adequately rank MD adherence.

Study limitations comprise firstly, a small sample size meaning the statistical tests would only have small power. A further limitation of this study is that our findings may not apply to the general population as the participants belonged to a selected population who may have a particular dietary behaviour due to their knowledge about their genetic disposition for breast cancer.

We will be using the German MEDAS in our main trial that aims to recruit 600 study participants. We decided to use the adherence to MD measured by the MEDAS score as one of 3 co-primary endpoints [31].

Conclusions

Despite the study limitations, we conclude that the present version of MEDAS could be a reasonable tool in determining adherence to a MD in German-speaking populations. This short screener is a valid tool for the rapid assessment of adherence to the MD that may also be useful not only for trials but also in clinical practice. The MEDAS score would allow an immediate feedback to study participants or patients regarding their adherence to MD.

Abbreviations

BMI: Body Mass Index; EPIC: European Prospective Investigation into Cancer and Nutrition; EDTA: ethylene diamine tetraacetic acid; FFQ: Food Frequency Questionnaire; HPLC: high performance liquid chromatography; hsCRP: High-sensitivity C-reactive protein; ICC: Intraclass correlation; ISPOR: International Society For Pharmacoeconomics and Outcomes Research; K: Cohen's Kappa; MEDAS: Mediterranean Diet Adherence Screener; MD: Mediterranean Diet; LIBRE: Lifestyle intervention in BRCA 1/2-mutation carriers; PREMED: PREención con Dieta MEDiterránea (PREvention with MEDiterranean Diet)

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Availability of data and materials

The raw data used for this study is shared within the study group.

Authors' contributions

KH and MY-D planned and designed the analysis, contributed to the acquisition of data, carried out the statistical analysis and interpretation of its results and drafted the manuscript. CE, MS, NE, MH, WV and MK have contributed to the acquisition of data, interpretation of the analysis results and revision of the manuscript critically for important intellectual content. SCB conceived this validation study, contributed to the acquisition of data, interpretation of the analysis results and revision of the manuscript critically for important intellectual content. All authors have read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

All women participated in the study voluntarily and gave written informed consent prior to study begin. They were informed that they can withdraw their consent and stop participation at any time without disclosing the reasons and without negative consequences for their future medical care. The responsible ethics review boards of all participating trial sites approved the study protocol (Reference number 5686/13 for the leading vote of the Klinikum Rechts der Isar of the Technical University of Munich).

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