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

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Submitted by:

Master of Science Maryam Yahiaoui-Doktor, née: Yahiaoui

born on 25th April 1974 in Tehran, Iran

Completed at:

Institute for Medical Informatics, Statistics and Epidemiology (IMISE), University of Leipzig

Supervisor:

Priv.-Doz. Dr. med. habil. Christoph Engel

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Yahiaoui-Doktor, Maryam

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Breast cancer is worldwide the most common cancer amongst women with 5-10% estimated to be inheritable. For women with germline pathogenic variants in *BRCA1 and BRCA2* genes, the lifetime risk of developing breast and ovarian cancer is higher than the general population (69-72% and 17-44%). Current options for women facing this risk are prophylactic surgery or intensive surveillance programmes.

Prospective studies have shown physical activity and healthy nutrition can reduce the risk of sporadic breast cancer. Therefore, a randomised clinical trial (LIBRE) was initiated to evaluate whether a lifestyle intervention in carriers of *BRCA1* and *BRCA2* mutations could lead to a decrease in incidence and mortality rates for breast cancer. The intervention consists of physical endurance training and the adoption of the Mediterranean Diet (MD).

The aim of the work presented in this thesis was to validate the German MEDAS. MEDAS was originally used in the Prevención con Dieta Mediterránea trial, in Spanish (published in English). It was translated from English into German for the LIBRE trial. For the validation, MEDAS was compared to the validated German Food Frequency Questionnaire (FFQ) and its associations with dietary intake biomarkers in the blood typical of the MD were analysed.

MEDAS was more sensitive than FFQ in detecting adherence to the MD, while item level agreement varied. Associations were seen between MEDAS questions and corresponding dietary intake biomarkers in the blood. The strongest association was between fish consumption and the fatty acids omega-3 and omega-6. It was concluded MEDAS could be useful for assessing the adherence to the MD in clinical practice or trials.

[1] Some references may occur in both the thesis and the publication.

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1. Background

Breast cancer is worldwide the most common cancer amongst females, affecting over 1.5 million women each year, and it is the first cause of cancer-related death among women (1). The situation is similar in Germany where 69,220 women were diagnosed with this disease in 2014 alone, while 18,136 died of it in 2015 (2). An estimated 5 to 10% of breast cancer incidences are hereditary, with a number of genes involved (3-5).

Inheriting a pathogenic variant (mutation) of certain genes is known to increase the risk of developing breast cancer. The first of the responsible genes to be discovered, and the most widely known, are the breast cancer susceptibility genes *Breast Cancer 1 and Breast Cancer 2* (*BRCA1* and *BRCA2*). They are both tumour suppressor genes, whose function is to control cell growth and repair damaged DNA. If both alleles of one of these genes themselves are defective, the gene cannot carry out its functions correctly, thus increasing the risk of tumour development, especially in the breast and ovaries in females.

Inheriting one defective copy means the person is predisposed to disease development, i.e. with just one further variation, the gene's functionality is lost. It has been shown that women who have inherited a pathogenic variant in one of these two genes have a higher lifetime risk of developing breast cancer. The cumulative risk of breast cancer to age 80 for mutation carriers was found to be 72% for *BRCA1* and 69% for *BRCA2*, and 44% and 17% for ovarian cancer, respectively (6).

Current options for these women are prophylactic surgery and intensive surveillance programmes. Prophylactic mastectomies almost eliminate the risk of developing breast cancer, while prophylactic bilateral salpingo-ophorectomy are thought to considerably reduce the risk of breast cancer and almost eliminate the risk of ovarian cancer in BRCA germline mutation carriers (7). This option however weighs heavily on those affected, as these are major irreversible operations with their own associated additional health risks (8, 9). As an alternative, intensive surveillance or breast cancer screening programmes allow regular monitoring of the health status of women at high risk, making early therapy and recovery possible. This option has its own drawbacks in that it can incur more costs and stress than is necessary for the women, healthcare providers and other stakeholders (10).

Additionally, there are non-genetic (environmental or lifestyle) risk-modulating factors that play a role in disease development. In order to identify these, one can look to risk factors

identified in sporadic breast cancer studies. The effect of such factors on *BRCA1* or *BRCA2* germline mutation carriers may then be determined through further studies.

1.1. Lifestyle factors and risk of sporadic breast cancer

Physical activity, nutrition and weight, regardless of age have been found to be amongst factors affecting the risk of sporadic breast cancer development (11, 12). It is estimated that the lifetime breast cancer risk in all women could be reduced by 30% through lifestyle measures such as weight control, exercise and moderating alcohol intake (13). Energy intake restriction and weight control (through diet regimen) have shown clearer effects on risk reduction, whereas the effects of specific dietary components have been more difficult to quantify (13). In short, exercise, nutrition and weight control are three related lifestyle factors combining to affect breast cancer risk.

Significant reduction of breast cancer incidence in both pre- and post-menopausal women through regular exercise has been shown in many prospective studies, reducing the risk on by 25% average (14). The risk of a relapse and mortality due to breast cancer have been shown to be reduced by around 24-40% for women who exercise more and regularly (15). Additionally, with more and regular exercise, breast cancer patients are likely to benefit from an enhanced quality of life, higher fitness levels and better tolerance of chemotherapy and its associated side effects (16-19).

The risk of breast cancer is increased significantly due to weight gain and obesity in both pre- and postmenopausal women (20, 21). Overall, up to 15% of sporadic breast cancer cases could be due to a weight gain of 2 kg or more from the age of 18 years onwards, and approximately 4.4% because of a weight gain of 2 kg or more following the onset of menopause (20).

As well as increasing the risk for primary tumour development, obesity is a predictive factor for both developing distant metastases (46% risk increase for BMI over 30) and mortality (38% risk increase for BMI over 30) as a result of breast cancer (22). There is also indication that BMI affects the effectiveness of breast cancer therapy, both chemo- and endocrine therapy having been less effective after 10 or more years for patients with BMIs greater than 30 (22). This trend has been found elsewhere; obesity in particular increases the risk of disease, one review of 82 studies on the topic finding poorer breast cancer survival results in association with obesity irrespective of age (23-26).

Weight gain results in shifting levels of insulin, glucose and fats in the body, which allow tumours to develop and progress, the complex biological mechanisms and pathways of which are not yet fully identified (27). To this end, several trials have explored the effects of particular diets and dietary components on the risk of breast cancer.

Compared with a usual diet group, a low-fat dietary pattern was found to lead to a lower incidence of deaths in breast cancer survivors (28). Another study found a 'prudent' diet – characterised by higher consumption frequency of dairy products, fruit and vegetables, wholemeal bread, fish and juices – was associated with lower risk for breast and lung cancer compared to fast-food or old traditional Polish diets (29). Elsewhere, a 'healthy' diet was among items of healthy behaviour, which reduced the risk of various cancers, including that of the breast (30). Consuming more vegetables and fruit was associated with decreased breast cancer risk in another recent study (31). Grilled meat and higher cholesterol intake on the other hand were found to increase breast cancer risk (32).

There are other lifestyle factors associated with breast cancer, although the focus of this work is diet. Alcohol consumption is one of these, here the general view is that avoiding overconsumption would be advantageous in reducing breast cancer risk (33). Tobacco consumption particularly increases the risk of disease in the years between menarche and the first full time pregnancy (24, 25). Managing and reducing stress are factors that also play a role, for instance cognitive behavioural intervention to manage stress could help increase immunologic resistance by regulating cortisol levels (34).

1.2. Mediterranean Diet

Willett et al. described "a food pyramid that reflects Mediterranean dietary traditions, which historically have been associated with good health" (35). This diet is characterised by plentiful consumption of plant foods; moderate amounts of dairy products, fish, poultry and eggs; and low amounts of red meat. Olive oil is the principal source of fat, while desserts are based on fruits, and wine may be consumed with meals in low to moderate amounts.

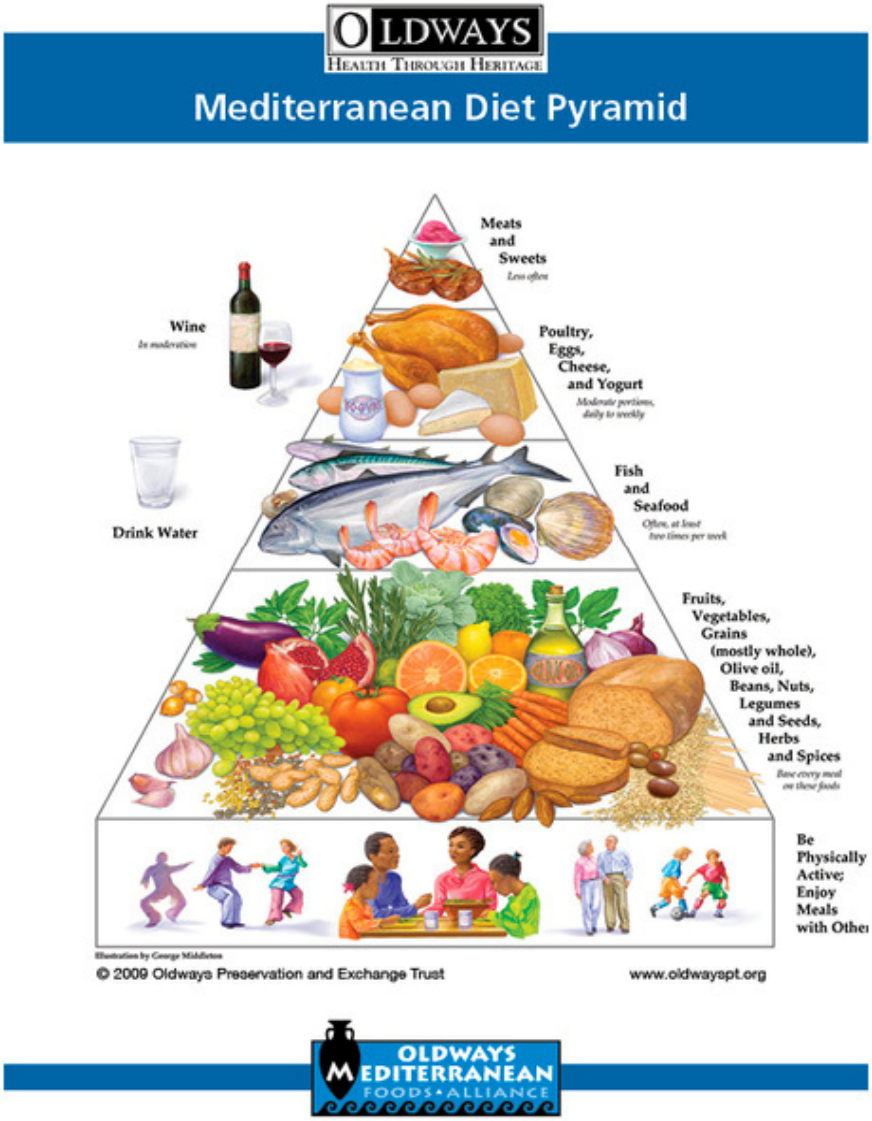

Figure 1 - The Mediterranean Diet pyramid - Courtesy of Oldways, oldwayspt.org

This nutritional base, combined with physical activity, is seen to have led to longer life expectancy and lower rates of several diseases, including some cancers, especially in Greece and southern Italy in the early 1960s. Elsewhere in the world, dietary patterns sharing the common characteristics of what has been defined as Mediterranean have been associated with better life expectancy and lower chronic diseases rates (36). Figure 1 illustrates the Mediterranean Diet (MD) alongside physical activity.

Some studies have looked into the association between the adherence to this dietary pattern and sporadic breast cancer risk. There are indications that the MD acts as a protective factor against breast cancer. For instance, pooled analyses of individual components of the MD found that its

protective effects appear to be most attributable to fruits, vegetables, and whole grains (37). The antioxidants and anti-inflammatory properties of the food items in the MD might explain its benefits against the development of many diseases including cancer, was the conclusion of another study (38). An increased risk of breast cancer was seen in women who consumed a pro-inflammatory diet, especially in postmenopausal years (39, 40).

The MD or a diet close to it – rich in fruits, vegetables, legumes, oily fish and vegetable oils – seem to be advantageous in the effort to reduce breast cancer risk (41-43). The biological mechanisms for cancer prevention or risk reduction associated with the MD have been linked to the favourable effect of a balanced ratio of omega-6 and omega-3 fatty acids and high amounts of fibre, antioxidants and polyphenols found in fruit, vegetables, olive oil and wine (44).

A review in 2015 concluded there to be insufficient data to reach a final conclusion about the effect of the MD on breast cancer risk in pre- and postmenopausal women, but that there was evidence suggesting the effect is protective (45). Often in the studies the level of adherence to the MD is quantified by a score (the MD score), which sums up the number of MD items or food groups consumed on a regular basis. A recent systematic review (2018) found results from analysing the effects of the MD on breast cancer risk using different versions of MD scores to be consistent, and suggest an inverse relationship with Oestrogen receptor-negative breast cancer (46). There have also been attempts to quantify the effect of the MD on changes in the risk of breast cancer development in some studies. The results were in accordance with the trend seen previously, showing a protective association between the MD with regards to breast cancer risk, with a risk reduction of up to 6% (37, 47-49).

1.3. Non-genetic risk factors for disease in *BRCA1* and *BRCA2* mutation carriers

As discussed, several factors are involved in the development of sporadic breast cancer. These include environmental and lifestyle factors, material exposure (e.g. chemicals, radiation, metals, etc.), activity, diet, alcohol and tobacco (50). Inferring from risk factors for sporadic breast cancer, it may be possible to undertake measures to reduce the risk of breast cancer development for women with germline pathogenic variants of *BRCA1* and *BRCA2*.

Previously, aspects such as the number of pregnancies, the year of birth, physical activity in youth, as well as breast feeding were found to affect the risk of disease development in *BRCA1*

and *BRCA2* mutation carriers (51-53). Additionally, BMI or height at different ages were seen to affect the risk of disease development in this population, just as for sporadic breast cancer patients (54, 55). Menopausal status modifies the association between body weight and breast cancer development risk in this population (56). It was also found that physical activity or exercise directly affects oestrogen levels and hormonally sensitive breast tissue, which can in turn influence the risk of disease development in *BRCA1* and *BRCA2* mutation carriers (57).

Controlling adult weight through diet is an important factor in the prevention of *BRCA* related breast cancer (58). Until now, a few studies have investigated the relationship between disease onset and particular food items in carriers of germline *BRCA1* and *BRCA2* mutations. For instance, it was concluded that consumption of vegetables and fruit might help reduce the risk of breast cancer in BRCA mutation carriers, while higher total energy intake, and coffee and alcohol consumption can increase this risk (59, 60). Soya consumption for instance, may reduce the risk of disease development in this population (61).

The effect of the MD on the risk of breast cancer has however thus far been investigated in very few studies in carriers of germline pathogenic variants of *BRCA1* and *BRCA2*. Bruno et al. have reported the initial results of their trial, which examines effects of the MD and physical activity in this population. The intervention group showed an improvement in their MD scores and Metabolic Syndrome (62).

Given the need for further research in this area, a clinical trial was designed and initiated for this group of women to understand better the viability of regular exercise and diet improvements as possible breast cancer prevention measures. This is the **L**ifestyle **I**ntervention Study in Women with Hereditary **Bre**ast and Ovarian Cancer (LIBRE) trial.

1.4. LIBRE trial

LIBRE is a prospective, open-label, randomised (1:1), controlled and multi-centre clinical trial, carried out in two phases (63). Its participants are women with a germline pathogenic variant in the *BRCA1* or *BRCA2* gene. The primary aim of LIBRE-1 has been to evaluate the feasibility of the design of the study, including the intervention method. A total of 68 participants were recruited in three centres of the German Consortium for Hereditary Breast and Ovarian Cancer (Cologne, Kiel and Munich) starting in 2014. This phase of the trial is currently in its follow-up stages, having been confirmed as feasible allowing the larger LIBRE-2 phase to ensue.

LIBRE-2 aims to recruit at least 600 participants and study as its primary endpoints the adherence to the MD, BMI and ventilatory threshold VT1 after one year of intervention (64). There are several secondary endpoints of the LIBRE-2 trial, some of which are: measurements on quality life, stress coping, fat calorie intake, physical activity and body fat content.

The intervention in the LIBRE study comprises a one-year endurance exercise programme combined with the adoption of the MD. The exercise part consists of home- and centre-based training, while the nutritional part includes courses and supermarket shopping trips on components of the MD. The intervention is divided into two parts, an intensive phase (the first three months) during which contact with participants is on a weekly basis and a light phase (the following nine months) when there is only telephone contact with participants every three months. The control group receive recommendations on a healthier lifestyle, including general advice on the importance of exercise and nutrition once. The nutritional advice is in accordance with the recommendations of the German Society of Nutrition.

Two food intake questionnaires – the Mediterranean Diet Adherence Screener (MEDAS) and the Food Frequency Questionnaire (FFQ) from the European Prospective Investigation into Cancer and Nutrition (EPIC) – are given to both the intervention and control groups. Both questionnaires are used to determine the dietary habits of the LIBRE participants and are described in more detail in the next two sections. They are given to the participants at Baseline, three months and then twelve months for both groups; plus at each yearly follow-up afterwards for up to 3 years. In LIBRE-1, the intervention group additionally answered MEDAS at six and nine months. The focus of this dissertation is on the intensive phase of the intervention, i.e. between the time of start of the intervention and three months later.

1.5. Mediterranean Diet Adherence Screener questionnaire

This is a questionnaire originally used in the Prevención con Dieta Mediterránea (PREDIMED) trial, in the Spanish language (65). Schröder et al. validated this original version of the MEDAS, which they published in the English language (66). For the LIBRE-1 study, MEDAS was translated from the English version into German using a method describe in detail in the next section. The usage context of the questionnaire was a short and rapid screener, for clinical practice, to determine the adherence to the pre-defined Mediterranean Diet as described by Willett et al. (35, 66).

The MEDAS questionnaire consists of 14 questions, which typify the MD. Each answer that matches the MD gets one point to build a total (sum) MD score of up to 14. Table 1 below lists the English questions and their point distributions.

Table 1- MEDAS questions in English

Question	+1 point	0 point
1. Do you use olive oil as the principal source of fat for cooking?	Yes	No
2. How much olive oil do you consume per day (including that used in frying, salads, meals eaten away from home, etc.)?	At least 4 tablespoons	Less than 4 tablespoons
3. How many servings of vegetables do you consume per day?	At least 2	Less than 2
4. How many pieces of fruit (including fresh-squeezed juice) do you consume per day?	At least 3	Less than 3
5. How many servings of red meat, hamburger, or sausages do you consume per day?	Less than 1	At least 1
6. How many servings (12 g) of butter, margarine, or cream do you consume per day?	Less than 1	At least 1
7. How many carbonated and/or sugar-sweetened beverages do you consume per day?	Less than 1	At least 1
8. Do you drink wine? How much do you consume per week?	At least seven cups	Less than seven cups
9. How many servings of pulses do you consume per week?	At least 3	Less than 3
10. How many servings of fish/seafood do you consume per week?	At least 3	Less than 3
11. How many times do you consume commercial (not homemade) pastry such as cookies or cake per week?	Less than 2	At least 2
12. How many times do you consume nuts per week?	At least 3	Less than 3
13. Do you prefer to eat chicken, turkey or rabbit instead of beef, pork, hamburgers, or sausages?	Yes	No
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?	At least 3	Less than 3

For the LIBRE-1 and 2 trials, MEDAS was complemented with pictures of foods that matched the questions, which is appended to this thesis.

1.5.1. Translation process

This translation was carried out by members of the project team as part of LIBRE-1, and followed the guidelines from the International Society of Pharmacoeconomics and Outcomes Research (67). The MEDAS was translated from its validated version (in English) into German, and then two native German speakers reviewed it. An English native speaker then translated this reviewed version back into English. A group of the study team then approved the back-translated version by comparing it to the original English version.

1.6. Food Frequency Questionnaire

This was the larger nutritional questionnaire used in the LIBRE trial, and was the questionnaire that MEDAS was compared to as part of the validation process. The FFQ was developed within the framework of the EPIC study. The FFQ (German version used in LIBRE) is a detailed 33 page, 148 item questionnaire on food habits twelve months prior to being administered (68-70).

It asks about general nutritional behaviour, before going into specific details on nutritional supplements and then portions and frequency of solid and liquid food groups' intake. The food groups comprise bread and cereals, milk and dairy products, fruit, raw vegetables, meat and fish to name but a few. Colour photos accompany items that are not consumed in normal household quantities to make understanding the portions easier. There are also specific questions on the type of cooking fats used, the frequency of consumption of sauces with fish or meat, the fat content of consumed milk products, the use of sugar and milk in coffee or tea and the seasonal consumption of fresh fruit and vegetables. At the end, a summary regarding food intake in summer and winter, plus weight and height of the participant is asked.

The German Institute of Human Nutrition (Deutsches Institut für Ernährungsforschung - DifE) administers and analyses data gathered from this questionnaire. The resulting dataset contains all answers from which, for the MEDAS validation, the relevant items were chosen.

2. Aim

The aim of the work presented in this thesis was to determine the suitability of the German version of MEDAS as a short and practical questionnaire for everyday clinical use to determine the level of adherence to the MD. In order to do this, MEDAS was compared to the larger, validated FFQ, which measures food intake in general.

Several measures of concordance were used to analyse item-level agreement between the 14 MEDAS questions and corresponding items from FFQ. These were the absolute agreement, Pearson's product-moment correlation, Cohen's kappa and intraclass correlation.

In order to see how the questionnaire scored the MD compared to one another, the Bland-Altman method was used. Subsequently, t-Test and multivariate regression analyses were used to explore whether MEDAS could specifically determine the adherence to the MD. In this step, β-carotene, fatty acids omega-3, omega-6 and omega-9, and high-sensitivity C-reactive protein (hs-CRP) were analysed for their associations with MEDAS questions regarding vegetables and fruits, olive oil, red meat, fish and nuts.

These analyses were carried out for the two time points Baseline and after three months. The results are presented in the following publication.

Hebestreit et al. BMC Cancer (2017) 17:341
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RESEARCH ARTICLE Open Access

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

Katrin Hebestreit[1†], Maryam Yahiaoui-Doktor[2†], Christoph Engel[2], Walter Vetter[3], Michael Siniatchkin[4], Nicole Erickson[5], Martin Halle[6,7], Marion Kiechle[8*] and Stephan C. Bischoff[1]

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

* Correspondence: marion.kiechle@tum.de
†Equal contributors
[8]Department of Gynecology and Center for Hereditary Breast and Ovarian Cancer, Women's Hospital Klinikum Rechts der Isar der, Technical University Munich (TUM), Gynaecology and Obstetrics, Ismaningerstrasse 22, 81675 Munich, Germany
Full list of author information is available at the end of the article

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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 Chi^2 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%)

[a]median (range)
[b]numbers (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

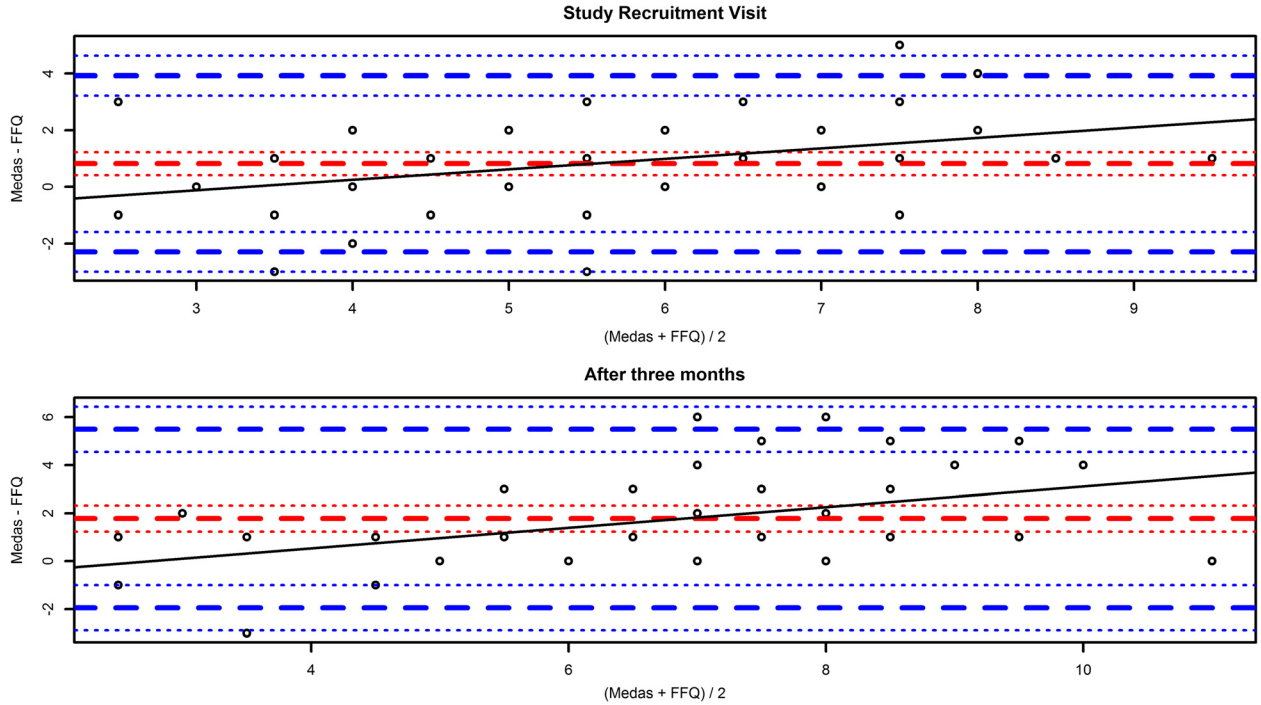

Fig. 1 Bland-Altman plots showing the differences between the MEDAS score aggregated from MEDAS and FFQ questionnaires at baseline and after 3 months. The *red dashed* and *dotted lines* indicate the mean bias and its 95% confidence interval. The *blue dashed* and *dotted lines* depict limits of agreement and their 95% confidence intervals

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

	Baseline ($n = 66$)			At 3 months($n = 54$)		
MEDAS food group association with dietary biomarker(s)	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 [μg/l]	859.7 (26)	889.3 (39)	0.868	487.8 (9)	918.9[1] (45)	**0.004**
fruit with						
β-carotene [μg/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

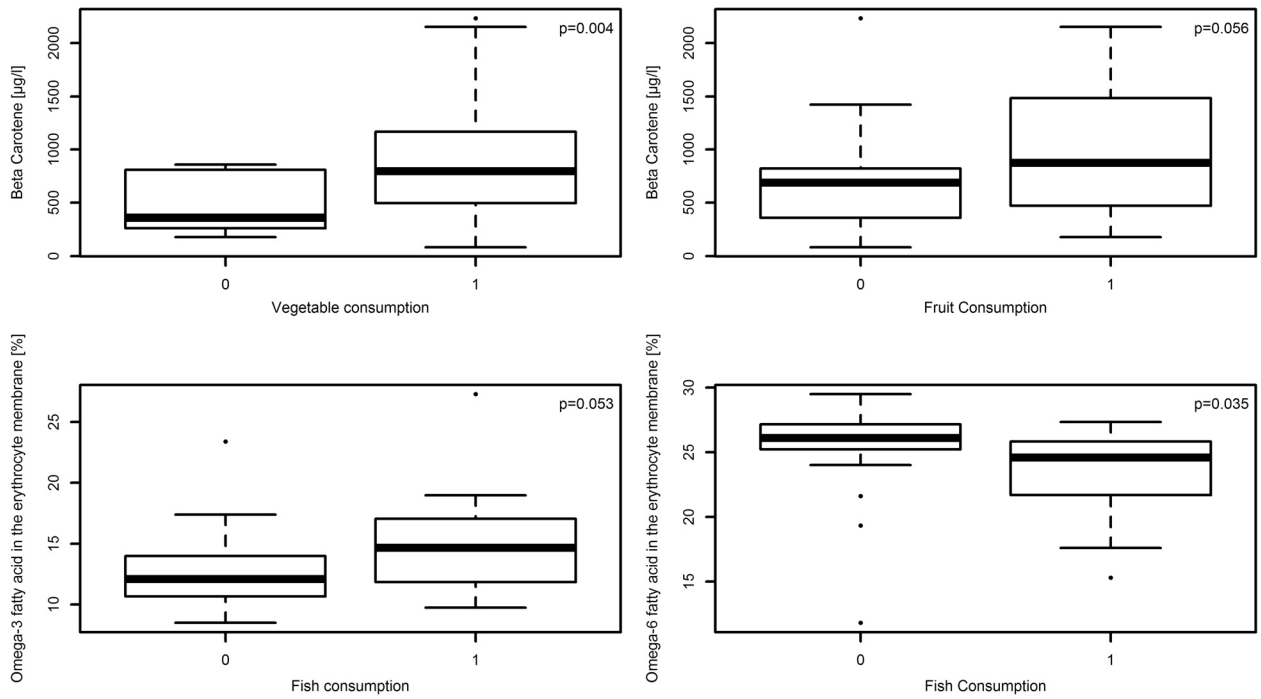

Fig. 2 Association of vegetable consumption (question 3 of the MEDAS questionnaire) and fruit consumption (question 4 of the MEDAS questionnaire) with β-carotene; and association of fish consumption (question 10 of the MEDAS questionnaire) with omega-6 fatty acids and omega-3 fatty acids after 3 months (V1) [0 = 0 point in the MEDAS question; 1 = 1 point in the MEDAS question]. The *p*-value was calculated using the t-test

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

	Baseline		At 3 months	
Dietary biomarker association with MEDAS food group	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 charachterisic 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. Takkumen 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; PREDIMED: PREvención con Dleta 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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Author details
[1]Institute for Nutritional Medicine, University of Hohenheim, Fruwirthstr. 12, 70593 Stuttgart, Germany. [2]Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Haertelstrasse 16–18, 04107 Leipzig, Germany. [3]Institute for Food Chemistry, University of Hohenheim, Fruwirthstr. 12, 70593 Stuttgart, Germany. [4]Institute for Medical Psychology and Sociology, University Hospital Schleswig-Holstein, Campus Kiel, Preusserstr. 1–9, 24105 Kiel, Germany. [5]Comprehensive Cancer Center (CCC LMU), Ludwig Maximilian University Munich, Campus Großhadern, Marchioninistr. 15, 81377 Munich, Germany. [6]Else Kroener-Fresenius Prevention Center, Klinikum rechts der Isar, Technical University Munich (TUM), Ismaningerstr. 22, 81675 Munich, Germany. [7]Department of Prevention and Sports Medicine, Klinikum rechts der Isar, Technical University Munich (TUM), Ismaningerstr. 22, 81675 Munich, Germany. [8]Department of Gynecology and Center for Hereditary Breast and Ovarian Cancer, Women's Hospital Klinikum Rechts der Isar der, Technical University Munich (TUM), Gynaecology and Obstetrics, Ismaningerstrasse 22, 81675 Munich, Germany.

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Summary

Thesis for obtaining the doctorate degree Dr. rer. med.

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

Submitted by: Maryam Yahiaoui-Doktor, née: Yahiaoui

Completed at:

Institute for Medical Informatics, Statistics and Epidemiology (IMISE), University of Leipzig

Supervised by:

Priv.-Doz. Dr. med. habil. Christoph Engel

June-2018

The most common cancer among women in Germany – and in the world – is breast cancer, of which 5-10% can be attributed to inherited pathogenic variants of certain genes. *BRCA1* and *BRCA2*, are two such genes, which act as tumour suppressors and mutations in which are known to increase the risk of breast cancer greatly. Current choices for women facing this risk are prophylactic surgery or intensive surveillance programmes.

There are however, non-genetic factors, for instance lifestyle-related, that are known to reduce the risk of sporadic breast cancer. Therefore, a clinical trial – LIBRE – was designed to explore the effects of some of these lifestyle changes in *BRCA1* and *BRCA2* germline mutation carriers. The trial is multi-centre, randomised, controlled and open-label. The one-year intervention consists of endurance sport training and the adoption of the Mediterranean Diet. The intervention is divided into two parts, an intensive (first three months) phase and a light phase

(the following nine months). In this trial two nutritional questionnaires are administered, the Food Frequency Questionnaire (FFQ) and Mediterranean Diet Adherence Screener (MEDAS). In the publication introduced in this thesis, the German version of MEDAS was validated, comparing it to the previously validated German FFQ. The translation and validation of MEDAS were done in the setting of the LIBRE study.

The validation was done in several steps, the first of which was item-level agreement analysis by means of absolute agreement, Pearson's product-moment correlation, Cohen's kappa and intraclass correlation. The Bland-Altman method was used to compare the Mediterranean Diet scores resulting from the questionnaires. Then the association of dietary intake biomarkers β-carotene, fatty acids omega-3, omega-6 and omega-9, and high-sensitivity C-reactive protein (hs-CRP) with corresponding MEDAS questions regarding vegetables and fruits, olive oil, red meat, fish and nuts was analysed using t-Tests and multivariate linear regressions. All analysis was done using data from Baseline and after three months.

Item-level agreement varied between questions, but was strongest where both questionnaires asked the questions similarly, e.g. the question on consumption of olive oil and nuts in general. On the other hand, the lowest agreement was seen where the MEDAS question was asked indirectly in FFQ, e.g. the question on daily portions of olive oil. The Bland-Altman analysis showed that mean Mediterranean Diet scores resulting from MEDAS were 15% higher than the scores from FFQ at baseline and 23% higher after three months. This meant that MEDAS is more sensitive to (has a bias) towards MD items in comparison to the FFQ.

Additionally, significant associations between dietary biomarkers in the blood and specific MD food groups (questions from MEDAS) were found. Consumption of more fish, i.e. at least 3 portions a week was associated with higher omega-3 and lower omega-6 fatty acids. More fruit and vegetable consumption showed an association with higher levels of β-carotene. In the analysis of the association of several food items together with dietary intake biomarkers, higher fish consumption again showed a significant association with higher omega-3 and lower omega-6 fatty acids.

In conclusion, the satisfactory agreement of MEDAS and FFQ, and the higher sensitivity of MEDAS to the MD speak for its suitability to measure adherence to the MD. Additionally, despite the low participant numbers and thus small statistical power, associations between MEDAS and relevant dietary intake biomarkers in the blood were found. This speaks for the

suitability of this translation of the MEDAS in determining the adherence to the MD in German-speaking populations.

The MEDAS German version as presented here is being used in the LIBRE-2 study. It is going to be used for another project, ENDORE, focusing on female infertility. The ENDORE project will run 2018 – 2021 with centres in Spain, Sweden, Estonia, Germany and USA. The German version will also be used in yet another project, the LIFE-Heart Follow-up study in Leipzig, which will run from 2018.

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Abbreviations

BRCA1 – breast cancer 1 gene

BRCA2 – breast cancer 2 gene

EPIC – The European Prospective Investigation into Cancer and Nutrition

DifE – Deutsches Institut für Ernährungsforschung

hs-CRP – high-sensitivity C-reactive protein

LIBRE **- L**ifestyle **I**ntervention study in women with hereditary **Bre**ast and ovarian cancer

MEDAS – Mediterranean Diet Adherence Screener

PREDIMED – Prevención con Dieta Mediterránea (Prevention with Mediterranean Diet) trial

Prof. Dr. Stephan C. Bischoff
Institut für Ernährungsmedizin
Fruwirthstr. 12, 70599 Stuttgart
☎ 0711 45924 101

MEDAS

Mediterranean Diet Adherence Screener – Fragebogen zur Mediterranen Kost

Übersetzt von ©Institut für Ernährungsmedizin, Universität Hohenheim, Stuttgart im Rahmen der LIBRE-Machbarkeitsstudie (Lebensstilintervention bei gesunden und erkrankten BRCA1/2 Mutationsträgerinnen und Frauen mit einem hohen Risiko für Brust- und Eierstockkrebs- Prospektive randomisierte multizentrische Feasibility-Studie)

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Deutsche Validierung: Hebestreit et al., BMC Cancer. 2017 May 18;17(1):341.

Bitte beachten Sie:

1. Eine Haftung des Instituts für Ernährungsmedizin im Zusammenhang mit der Nutzung des Fragebogens ist ausgeschlossen.

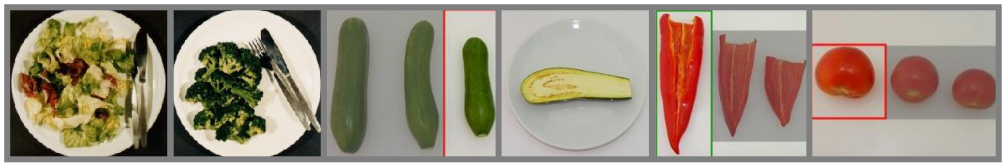
2. Bei Publikationen, die sich auf Daten oder Informationen beziehen, die mit Hilfe dieses Fragebogens generiert wurden, ist auf die LIBRE-Studie, das Institut für Ernährungsmedizin an der Universität Hohenheim (z.B. „Acknowledgment“) sowie die o.g. Validierungsstudie hinzuweisen.

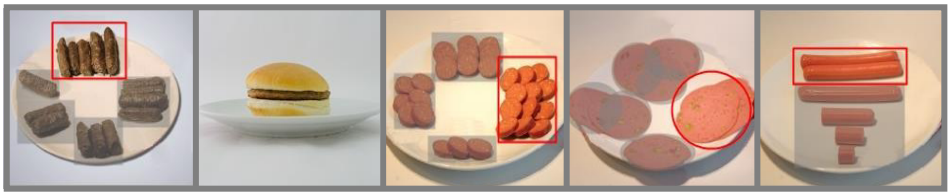
3. Der Fragebogen darf nicht an Dritte weitergegeben werden.

Auswertung:
Jede Frage wird mit 1 oder 0 Punkten bewertet. Die Antworten der linken Spalte werden mit einem Punkt gerechnet, die Antworten der rechten Spalte mit 0 Punkten. Anschließend wird die Gesamtsumme aller Fragen gebildet. Bitte beachten Sie, dass der Fragebogen nicht berücksichtigt, ob sich jemand vegetarisch ernährt. Falls deshalb Fragen ausgelassen werden, kann das Ergebnis auch prozentual angegeben werden.

Prof. Dr. Stephan C. Bischoff
Institut für Ernährungsmedizin
Fruwirthstr. 12, 70599 Stuttgart
☎ 0711 45924 101

1	Verwenden Sie in der Küche hauptsächlich Olivenöl?	ja	☐	nein	☐
2	Wie viel Olivenöl konsumieren Sie insgesamt **am Tag** (einschließlich dem Gebrauch zum Braten, zur Zubereitung von Salaten und Mahlzeiten und bei Restaurantbesuchen)?	mind. 4 Esslöffel	☐	weniger als 4 Esslöffel	☐
3	Wie viele Portionen frisches Gemüse (z.B. Eisbergsalat oder Spinat) konsumieren Sie **pro Tag**?	mind. 2 (davon 1 als Salat od. in Form von Rohkost)	☐	weniger als 2	☐
4	Wie viele Portionen Obst (einschließlich Fruchtsäfte) konsumieren Sie **pro Tag**?	mind. 3	☐	weniger als 3	☐
5	Wie viele Portionen rotes Fleisch, Hamburger, Wurst bzw. Wurstaufschnitte konsumieren Sie **pro Tag**?	weniger als 1	☐	mind. 1	☐
6	Wie viele Portionen Butter, Margarine oder Sahne konsumieren Sie **pro Tag**?	weniger als 1	☐	mind. 1	☐
7	Wie viele Portionen zuckerhaltige Getränke (Erfrischungsgetränke, Cola, Energydrinks, Eistee, Bionade, etc.) konsumieren Sie **pro Tag**?	weniger als 1	☐	mind. 1	☐





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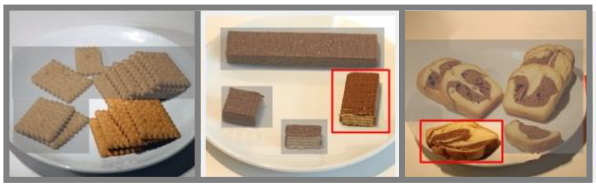
Institut für Ernährungsmedizin
Fruwirthstr. 12, 70599 Stuttgart
☎ 0711 45924 101

8	Wie viel Wein konsumieren Sie pro Woche?	mind. 7 Gläser	☐	weniger als 7 Gläser	☐
9	Wie viele Portionen Hülsenfrüchte (z.B. Bohnen, Erbsen, Linsen) konsumieren Sie **pro Woche**? 	mind. 3	☐	weniger als 3	☐
10	Wie viele Portionen Fisch oder Meeresfrüchte konsumieren Sie **pro Woche**?	mind. 3	☐	weniger als 3	☐
11	Wie viele Portionen Süßigkeiten (z.B. Schokolade, Bonbons, Gummibärchen) oder fertige (nicht selbstgebackene) Back - und Süßwaren wie Kuchen, Plätzchen, Kekse oder Pudding konsumieren Sie **pro Woche**? 	weniger als 3	☐	mind. 3	☐
12	Wie viele Portionen Nüsse (einschließlich Erdnüsse) konsumieren Sie **pro Woche**? 	mind. 3	☐	weniger als 3	☐
13	Bevorzugen Sie Hähnchen, Pute oder Kaninchen vor Rind, Schwein, Hamburger oder Wurstwaren?	ja	☐	nein	☐
14	Wie oft **pro Woche** konsumieren Sie Nudeln, Reis, Gemüse oder andere Gerichte, die mit einer Sauce aus Tomaten, Knoblauch, Zwiebeln oder Lauch, und mit Olivenöl zubereitet wurden?	mind. 2 Mal	☐	weniger als 2 Mal	☐
	Gesamtpunktzahl				

Statement on own contributions

Maryam Yahiaoui-Doktor is joint first author of the following publication:

Hebestreit K, Yahiaoui-Doktor M, Engel C, Vetter W, Siniatchkin M, Erickson N, Halle M, Kiechle M, Bischoff SC.
Validation of the German version of the Mediterranean Diet Adherence Screener (MEDAS) questionnaire.
BMC Cancer. 2017 May 18;17(1):341. doi: 10.1186/s12885-017-3337-y.

Maryam Yahiaoui-Doktor's own contributions to this work were as follows:

She carried out all parts of the statistical analysis. She was responsible for the selection of appropriate statistical methods for major parts of the data analysis. Moreover, she acquired and prepared the data for the analysis (except the data from the Food Frequency Questionnaire, FFQ). She wrote and created parts of the first draft of the manuscript, which were *Statistical analysis*, *Results* text, parts of the *Discussion* text, the *Results tables* and the *Figures*. She was responsible for correcting the language of the final manuscript.

Name: Univ. Prof. Dr. Marion Kiechle

Signature:

Date: March 2nd, 2018

Statement on own contributions

Maryam Yahiaoui-Doktor is joint first author of the following publication:

Hebestreit K, Yahiaoui-Doktor M, Engel C, Vetter W, Siniatchkin M, Erickson N, Halle M, Kiechle M, Bischoff SC.
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Name: Dipl.-Ernährungswissenschaftlerin Katrin Hebestreit

Signature: K Hebestreit

Date: 01/03/2018

Statement on own contributions

Maryam Yahiaoui-Doktor is joint first author of the following publication:

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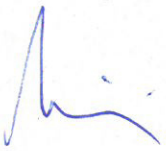
Name: Prof. Dr. Stephan C. Bischoff

Signature: 

Date: 7. May 2018

Statement on own contributions

Maryam Yahiaoui-Doktor is joint first author of the following publication:

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Name: Univ.-Prof. Dr. med. Martin Halle

Signature:

Date: March 2, 2018

Statement on own contributions

Maryam Yahiaoui-Doktor is joint first author of the following publication:

Hebestreit K, Yahiaoui-Doktor M, Engel C, Vetter W, Siniatchkin M, Erickson N, Halle M, Kiechle M, Bischoff SC.
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Name: Nicole Erickson M.Sc, RD

Signature: 

Date: 1.03.18

Statement on own contributions

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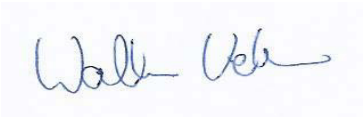
Name: Prof. Dr. Walter Vetter



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Date: March 2, 2018

Statement on own contributions

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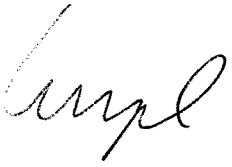
Name: Priv.-Doz. Dr. med. habil. Christoph Engel

Signature: 

Date: 30-MAY-2018

Statement on own contributions

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Erklärung über die eigenständige Abfassung der Arbeit

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar eine Vergütung oder geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren. Die aktuellen gesetzlichen Vorgaben in Bezug auf die Zulassung der klinischen Studien, die Bestimmungen des Tierschutzgesetzes, die Bestimmungen des Gentechnikgesetzes und die allgemeinen Datenschutzbestimmungen wurden eingehalten. Ich versichere, dass ich die Regelungen der Satzung der Universität Leipzig zur Sicherung guter wissenschaftlicher Praxis kenne und eingehalten habe.

.....	.....
Datum	Unterschrift

Curriculum Vitae

Name Maryam Yahiaoui-Doktor

Birth 25/4/1974 in Tehran, Iran

Professional experience

Biometrician and Computer Scientist, University of Leipzig, Leipzig	2/2010 - now
Programme and Project Manager, dunnhumby Ltd, London	2/2006 – 6/2008
Freelance Environmental and Energy Consultant	9/2005 – 1/2006
Lecturer, David Game College, London	4/2003 – 9/2004
Project Manager, Coutts Private Bank, London	3/2002 – 12/2002
IT Consultant and Project Manager, Brokat Technologies, London	8/2000 – 2/2002
IT Manager, Specialized Travel Ltd., London	4/1999 – 7/2000
Team Leader – Customer Services, Demon Internet, London	6/1996 – 8/1997

University Education

Environmental Technology – MSc, Imperial College, London	10/2004 – 9/2005
Computer Science – MSc, Birkbeck College, London	9/1997 – 8/1998
Law – CPE, London Guildhall University, London	8/1995 – 6/1996
Physics – BSc, Imperial College, London	10/1992 – 6/1995

Languages

German, English, Persian and French – spoken and written fluency

Spanish – middle level spoken and written fluency

List of other publications by Maryam Yahiaoui-Doktor

Clinical comparison of liquid-based and conventional cytology of oral brush biopsies: a randomized controlled trial. Olms C, Hix N, Neumann H, Yahiaoui-Doktor M, Remmerbach TW. Head & Face Medicine. 2018 May 28 14:9, doi: 10.1186/s13005-018-0166-4
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Correlates of satisfaction with pain treatment in the acute postoperative period: results from the international PAIN OUT registry. Schwenkglenks M, Gerbershagen HJ, Taylor RS, Pogatzki-Zahn E, Komann M, Rothaug J, Volk T, Yahiaoui-Doktor M, Zaslansky R, Brill S, Ullrich K, Gordon DB, Meissner W. Pain. 2014 Jul;155(7):1401-11. doi: 10.1016/j.pain.2014.04.021.
Patients' perception of postoperative pain management: validation of the International Pain Outcomes (IPO) questionnaire. Rothaug J, Zaslansky R, Schwenkglenks M, Komann M, Allvin R, Backström R, Brill S, Buchholz I, Engel C, Fletcher D, Fodor L, Funk P, Gerbershagen HJ, Gordon DB, Konrad C, Kopf A, Leykin Y, Pogatzki-Zahn E, Puig M, Rawal N, Taylor RS, Ullrich K, Volk T, Yahiaoui-Doktor M, Meissner W. J Pain. 2013 Nov;14(11):1361-70. doi: 10.1016/j.jpain.2013.05.016.

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