EVIDENCE-BASED CASE REPORT

Dementia Risk Reduction in Cognitively Normal Elderly Receiving Mediterranean Diet

Muhammad K. Azwar,[1]* Czeresna H. Soejono[2]

[1]Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[2]Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia

*Corresponding author: khifzhon@gmail.com
Received 2 May 2019; Accepted 3 December 2019
DOI: 10.23886/ejki.7.10491.

Abstract

Studies showed cognitive health improvement with mediterranean diet (MD). It is important to find out the benefit in dementia prevention. Relevant meta-analysis and randomised controlled trials pertaining to MD impact on dementia risk reduction in cognitively normal elderly were collected. The comprehensive search relied on databases Pubmed and Cochrane with keywords MD and dementia. Results of methodological quality assessment of three studies utilising Oxford Centre for Evidence Based Medicine year 2011 tools, showed that the studies were valid and applicable. Neuroprotective effect was different in group with the highest adherence to the diet in study 1 with adjusted hazard ratio (HR) of 0.67 (95% CI 0.52-0.88, p=0.004). In study 2 none were diagnosed with dementia in all three groups receiving MD with extravirgin olive oil (EVOO), diet with nuts, and control group. In comparison with the control group in study 3, number needed to treat (NNT) was 13.29 for group with EVOO (absolute risk reduction/ ARR = 7.5% [95%CI 1.09%-13.95%]) and was 10.79 for group with nuts (ARR = 9.2% [95%CI 2.88%-15.65%]). Long-term MD may be beneficial to reduce dementia rate. Neuroprotective effect is achievable only with the highest adherence (p=0.004). Gado-gado modification in Indonesian diet is desirable.
***Keywords**: dementia, mediterranean diet, risk reduction, prevention.*

Penurunan Risiko Demensia pada Usia Lanjut Berfungsi Luhur Normal dengan Diet Mediterania

Abstrak

Diet mediterania dapat mempertahankan fungsi kognitif berdasarkan beberapa penelitian. Manfaatnya terhadap pencegahan demensia perlu diketahui. Studi ini mengumpulkan meta-analisis dan uji acak dengan kontrol mengenai pengaruh diet mediterania terhadap penurunan risiko demensia pada usia lanjut (lansia) dengan fungsi luhur normal. Sumber data elektronik Pubmed dan Cochrane digunakan dengan kata kunci mediterranean diet dan dementia. Hasil dari penilaian kualitas studi dengan metode Oxford Centre for Evidence Based Medicine 2011 terhadap tiga studi terpilih menunjukkan bahwa studi tersebut valid dan dapat diterapkan. Efek neuroprotektif berbeda signifikan pada kelompok dengan tingkat ketaatan tertinggi pada diet mediterania dalam penelitian pertama dengan hazard ratio (HR) 0,67 (95% CI 0,52-0,88, p= 0,004). Pada penelitian kedua, tidak ada yang terdiagnosis demensia pada akhir penelitian pada ketiga kelompok, yakni kelompok diet dengan tambahan minyak zaitun ekstravirgin, kelompok dengan tambahan kacang-kacangan (kelompok 2), serta kelompok kontrol. Mekipun demikian penelitian ketiga menunjukkan number needed to treat (NNT) 13,29 pada kelompok minyak zaitun ekstravirgin (absolute risk reduction/ ARR = 7,5% [95%CI 1,09% - 13,95%]) dan pada kelompok 2 NNT 10,79 (ARR = 9,2% [95%CI 2,88%-15,65%]) dibandingkan kontrol. Diet mediterania jangka panjang dapat menurunkan angka demensia. Efek neuroprotektif hanya dapat dicapai dengan ketaatan tinggi terhadap diet (p=0,004). Pada diet Indonesia, modifikasi gado-gado dapat dipertimbangkan.
***Kata kunci:** demensia, diet mediterania, penurunan risiko, pencegahan.*

Introduction

Dementia is a clinical syndrome of cognitive impairment.[1] It is also called major neurocognitive disorder that interferes independence in patient's daily activities.[2] In the United States, Alzheimer's disease (AD) as the most common type of dementia is the third most expensive disorder after cancer and coronary heart disease. Not only is it a financial burden, one-third of caregivers of dementia patient have subsequent depression. Caregiver provision and severity-related institutionalisation of the patients also affect the expenditure. As the disease progresses, informal caregivers or family members spend time more on the patients. Overall, the economic, health care and social impact of dementia are enormous.[3] If the onset of dementia were delayed by five years, the prevalence of dementia would be halved.[4]

The current uptrend in life expectancy with increasing number of ageing population in low-and middle-income countries may suggest the expected higher prevalence of dementia. Indonesia will be one of six nations in the world with the number of individuals aged 80 years and above exceeding one million by 2050.[5] Multimodal strategies to prevent the occurrence of dementia are currently developed, including exercise, medication, and diet modification.[4]

Mediterranean diet (MD) has been tried in dementia prevention strategies.[4] This type of diet is protected by United Nations Educational, Scientific and Cultural Organization (UNESCO),[6] although in many studies the definition of MD is not identical compared to the traditional MD in 1960s.[7] The diet regimen contains 1-13 serves of cereals, up to 8 serves of olive oil, 3-9 serves of vegetables, and half to two serves of fruit on a daily basis.[8]

It is of great interest to find out whether MD is beneficial in dementia risk reduction. Thus, the research question would be "In cognitively normal elderly, does MD prevent from having dementia?" The patient is cognitively intact ≥60 year-old patient and the intervention is MD. The comparison group should be cognitively intact elderly who do not receive MD, whereas dementia risk reduction is the outcome of interest.

Clinical Case

During a home visit, 73-year-old male patient was diagnosed with bilateral knee osteoarthritis, dyslipidaemia, hypertension, chronic venous insufficiency and obesity. Patient has no history of diabetes mellitus, despite the family history of such disorder. In spite of having multimorbidity, he was still cognitively normal, with mini mental screening examination (MMSE) score being thirty and geriatric depression scale (GDS) score being zero. Patient routinely exercises and attends physiotherapy sessions. He has history of smoking and his diet regimen includes multiple portions of vegetables and fruit, 125 mg of rice twice daily, with rare occasion of including olive oil.

MD is a type of healthy diet, which is also rich in vegetable. Doctor is questioning whether a cognitively normal ≥60 years old patient may benefit from MD to reduce risk of dementia, formulation of the research, and evidence research strategy.

Methods

A comprehensive literature searching was conducted from 16–31 August 2018 utilising electronic databases Cochrane and Pubmed with keywords including *Mediterranean diet* and *Dementia*. '"Mediterranean diet" in Title Abstract Keyword AND "Dementia" in Title Abstract' were used on Cochrane and yielded 26 hits on 2 August 2018 at 18.09 hrs GMT+7. One study was selected from Cochrane. On the other hand, the keywords '(mediterranean diet [MeSH Terms]) AND dementia [MeSH Terms]' were used on Pubmed and yielded 87 hits on 12 August 2018 at 17.51 hrs GMT+7. Two studies were selected from Pubmed hits.

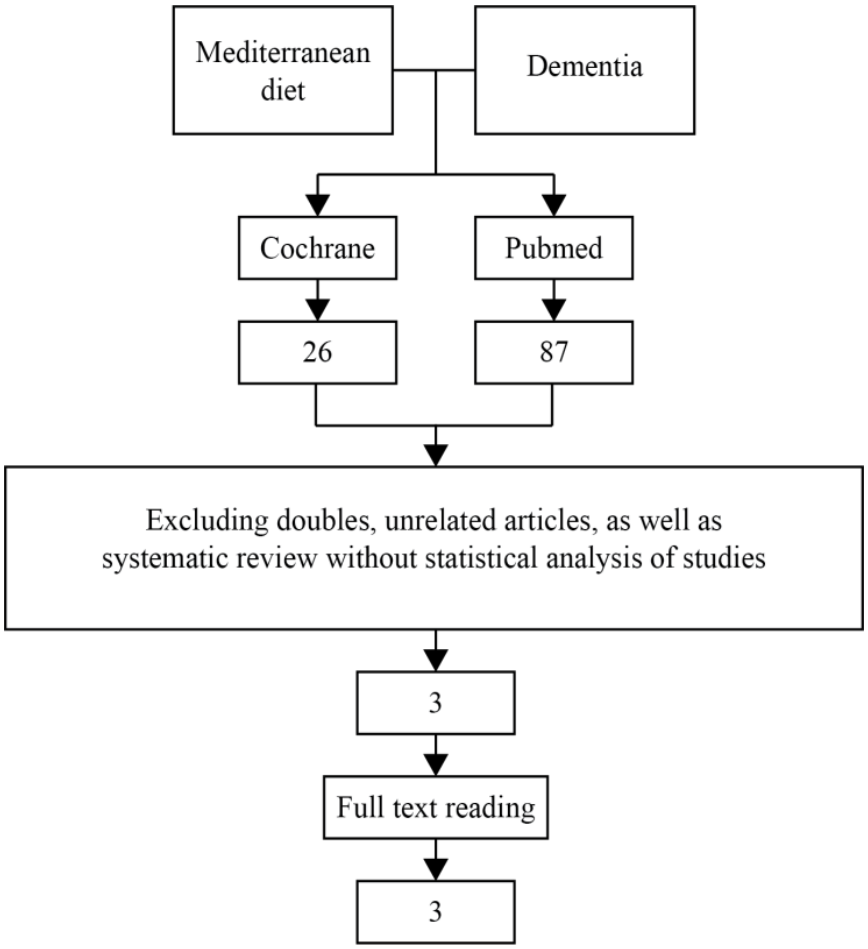

Figure 1. Searching Strategy for Relevant Evidence Followed by Results

Inclusion criteria consist of (1) randomized controlled trial (RCT) and meta-analysis; (2) population of patients without dementia; (3) received MD as treatment; (4) control group who did not receive MD; (5) beneficial effect of MD as outcome. According to those criteria, 113 articles were found. Afterwards, studies were selected to avoid doubles and unrelated articles, as well as not including systematic review with no further statistical analysis, see Figure 1.

Three included studies were further analysed for methodological quality using Oxford Centre for Evidence Based Medicine year 2011 including validity, importance and applicability. The characteristics of each study can be seen in Table 1.

Table 1. Characteristics of the Included Studies for Critical Analysis

Article	Study Design	Level of Evidence	PICO(s)	Study Participants (included articles in meta-analysis)
Singh et al.[9] 2014	Systematic review and meta-analysis	2A (including RCT and cohort studies)	P: Cognitively normal to mild cognitive impairment participants I: MD C: Other diet except MD O: Cognitive impairment (mild cognitive impairment/ MCI or AD	Five articles were included, three were from the US, and the two others were from France and Australia. Participants in the studies were all ≥65 years old, except in one study with age range 60-64 years. In the studies, there were cognitively normal group and group with MCI.
Valls-Pedret et al.[10] 2015	Randomised control trial	1B	P: Cognitively healthy participants I: MD supplemented with EVOO (1L per week) or MD supplemented with mixed nuts (30 g/day) C: Control diet with advice to reduce dietary fat O: Rates of cognitive change over time based on neuropsychological test battery	Experiment group: 127 cognitively healthy participants were assigned to MD with additional EVOO. 113 cognitively healthy participants were assigned to MD with additional nuts. Control group: 97 cognitively healthy patient received control diet with advice to reduce dietary fat
Martínez-Lapiscina et al[11] 2013	Randomised control trial	1B	P: Community-dwelling women (60-80 years) and (55-80 years) with either type-2 DM or ≥3 major cardiovascular disease (CVD) risk factors (overweight, dyslipidaemia, hypertension, smoking, and family history of premature CVD) without dementia I: MD supplemented with EVOO (1L per week) or MD supplemented with mixed nuts (30 g/day) C: low-fat diet (following AHA guidelines) O: Cognitive assessment, incidence of dementia and MCI.	Experiment group: 96.2% of 2543 participants were successfully followed after receiving MD with EVOO, and 92.1% of 2454 were followed in the group receiving MD with mixed nuts. Control group: 82.7% of 2450 were assigned to control diet

Results

The results of meta-analysis critical appraisal can be seen in Table 2. The critical appraisal result of RCT is shown in Table 3a and Table 3b with the former being validity analysis and the latter being the analysis of importance and applicability.

Table 2. Critical Appraisal of Meta-Analysis

Parameters	Singh et al[9]
What question (PICO) did the systematic review address?	P: Cognitively normal to MCI participants I: MD C: Other diet except MD O: Cognitive impairment
Is it unlikely that important, relevant studies were missed?	No. Comprehensive search was done utilising 6 databases until November 2012 without language limitation. Expert librarian was in charge of searching strategy design. In addition, hand search of conference proceedings of psychiatry, neurology and dementia organisations starting from 5 years before the study.
Were the criteria used to select articles for inclusion appropriate?	Yes. Inclusion criteria are only RCT as well as prospective cohort studies with at least one year follow up. This signified 2A level of evidence of the study. Other types of studies were excluded.
Were the included studies sufficiently valid for the type of question asked?	Yes. The studies were sufficiently valid for the question asked.
Were the results similar from study to study?	Yes. The results are similar from study to study.
How and what were the results?	Nine-point-scale mediterranean diet score (MeDi score) were used for quantification of adherence to the diet. Score of 6 or more was considered high adherence, whereas score of 4-5 and below 4 indicated middle and low adherence, respectively. The results showed that neuroprotective effect of MD was significantly different in highest diet tertile group with adjusted HR of 0.67 (95% CI 0.52-0.88, p=0.004), although the difference is not statistically significant for middle diet tertile group and low MD adherence score. MD with highest adherence had 33% lower risk of MCI or AD, compared to those with lowest adherence. Cognitively normal subject with high adherence to the diet had 22% less and 36% less risk of developing MCI and AD, respectively.

Table 3a. Critical Appraisal of Randomized Clinical Trial: Validity

Parameters	Valls-Pedret et al[10]	Martínez-Lapiscina et al[11]
What question (PICO) did the study ask?	P: Cognitively healthy participants I: MD supplemented with EVOO(1L/wk) or MD with mixed nuts (30g/d) C: Control diet with advice to reduce dietary fat O: Rates of cognitive change over time based on neuropsychological test battery	P: Community-dwelling women (60-80 years) and (55-80 years) with either type-2 DM or ≥3 major CVD risk factors (overweight, dyslipidaemia, hypertension, smoking, and family history of premature CVD) without dementia I: MD supplemented with EVOO (1L/wk) or MD with mixed nuts (30g/d) C: low-fat diet (following AHA guidelines) O: Cognitive assessment, incidence of dementia and MCI
Was the assignment of patients to treatments randomised?	Yes. Randomisation utilised computer-generated random-number sequence in blocks of 50 participants balanced by age (<70 and ≥70 years) and sex.	Yes. Randomisation utilised computer-generated random-number sequence to allocation ratio 1:1:1 to three groups.
Were the groups similar at the start of the trial?	Yes. Groups are similar except in terms of age and baseline HDL-C level. Participants in MD with additional EVOO is significantly older than control group, but baseline HDL-C level of EVOO is significantly higher compared to control group.	Unknown. The initial characteristic comparison of each intervention and control group at the start of the trial was not shown in the study.
Aside from the allocated treatment, were groups treated equally?	No. Quarterly education on how to adhere to diet regimen was only given to experiment groups. On the other hand, control group only received yearly visit for low-fat initially, although protocol amendment in the middle of the study changed the frequency of visit to be similar for all study groups. The median follow-up years for all groups were 4.1 years.	No. Quarterly education was only given to experiment groups, but not to control group. Mean follow-up time was 6.5 years for all groups.
Were all patients who entered the trial accounted for? And were they analysed in the groups to which they were randomised?	No. Initially 447 participants were randomised into olive oil (n=155), nuts (n=147) and control group (n=145). However, 25, 34, and 48 participants were lost to follow-up in olive oil, nuts, and control group. The loss was due to loss of contact, illness, death, refusal to get retested, and withdrawal. Not all participants were included in analysis in follow-up period due to exclusion related to depression which accounts for 3 of 130 olive oil group, 1 of 113 nuts group and 2 of 97 control group.	No. Initially 1055 participants were randomised into olive oil (n=351), nuts (n=352) and control group (n=352). However, 27, 29, and 30 participants were lost to follow-up caused by various reasons in olive oil, nuts, and control group, respectively. Not all participants were included in analysis following follow-up period because of refusal to participate and ineligibility. Those who were excluded from the analysis were 100 of 324 olive oil group, 157 of 323 nuts group and 190 of 321 control group.
Were measures kept “blind” to which treatment was received?	No. It is a single-blinded trial. Researchers and general practitioners were blinded.	No. It is a single-blinded trial. Researchers and general practitioners were blinded. Double-blind long-term trials in nutrition are said to be impossible.
Conclusion		**Valid**

Table 3b. Critical Appraisal of Randomized Clinical Trial: Importance and Applicability

Parameters	Valls-Pedret et al[10]	Martínez-Lapiscina et al[11]
Do these result apply to your patient?	Yes. The included subjects were cognitively healthy elderly.	Yes. The included subjects were community-dwelling elderly without dementia but with major cardiovascular risk factors.
How great would the potential benefit of therapy actually be for your individual patient?	Among 130, 113, and 97 participants in olive oil, nuts, and control group, none of them were diagnosed with dementia at the end of follow-up phase. Nevertheless, 17 of the olive oil group participants and 8 of the nuts group had mild MCI at the end of the study observation. On the other hand, 12 participants in control group had MCI. The result was not statistically significant (p=0.28)	Among 224, 166, and 132 participants in olive oil, nuts, and control group, there are 35 cases of incident dementia. (12 in olive oil group; 6 in nuts group; 17 in control group). NNT was 13.29 for group with MD and olive oil (ARR = 7.5% [95%CI 1.09% - 13.95%]). NNT was 10.79 for group with MD and additional nuts (ARR = 9.2% [95%CI 2.88% - 15.65%]). However, significance level was not provided by the authors.significance level of the difference in dementia rate when comparing the experiment and control group, as the RCT included in this case report did not provide such data
Are your patient's values and preferences satisfied by the regimen and its consequences?	Author and patient had clear assessment of the values and preferences, and they are met by this regimen.	
Conclusion	**Applicable**	

Singh et al[9] conducted systematic review and meta-analysis of studies in 2014 comprised of selected randomised clinical trials (RCTs) and cohort studies with at least one year of follow up. Five included studies were obtained from major databases and hand-searched proceedings until November 2012. Singh B, et al utilised 9-point-scale MeDi score for quantification of adherence to the diet. Score of 6 or more was considered high adherence, whereas score of four to five and below four indicated middle and low adherence, respectively. The results showed that neuroprotective effect of MD was significantly different in highest diet tertile group with adjusted hazard ratio (HR) of 0.67 (95% CI 0.52-0.88, p=0.004), although the difference is not statistically significant for middle diet tertile group and low MD adherence score.

A more recent RCT published in 2015 not included in the aforementioned meta-analysis showed beneficial cognitive changes following median follow-up 4.1 years. Valls-Pedret et al[10] grouped the participants into three groups, namely MD plus EVOO group (n=130), MD plus nuts group (n=113), and control group receiving advice regarding dietary fat reduction. The study revealed significantly better score in colour trail test part 2 (p=0.04) and Rey auditory verbal learning Test (RAVLT) in the treatment group receiving MD plus EVOO (p=0.049). The results of other tests, including MMSE, verbal fluency, digit span forward and backward, as well as colour trail test part 1, were not significantly changed from baseline result in the experiment groups when compared to the control diet group. The protective effect of MD against cognitive decline and AD was proven in this study, which is similar to the results of several longitudinal evidence. MD plus EVOOgroup had significant improvement in frontal and global cognition composites ($p<0.05$), whereas the nuts group had significant improvement in memory composite ($p<0.01$) compared to the control group. None of the participants in all groups had dementia at the end of observation. Nevertheless, 17 of the EVOO group participants and eight of the nuts group participants had mild cognitive impairment (MCI) at the end of the study observation. On the other hand, twelve participants in control group had MCI (p=0.28).[10]

Similarly, Martínez-Lapiscina et al[11] grouped the participants into three groups in the PREDIMED-NAVARRA randomised trial article

published in 2013. The groups were MD plus EVOO group (n=224), MD plus nuts group (n=166), and control group allocated to low-fat diet (n=132). In multivariate regression analysis, the adjusted means of clock drawing test (CDT) and mini mental state examination (MMSE) were significantly higher in the EVOO group compared with the control group (+0.51 [95%CI +0.20 – +0.82], p=0.001 for CDT; +0.62 [95%CI +0.18 - +1.05], p=0.005 for MMSE). The results were significantly higher in similar fashion in the nuts group (+0.33 [95%CI +0.003 - +0.67], p=0.048 for CDT; +0.57 [95%CI +0.11 - +1.03], p=0.015 for MMSE). After 6.5-year follow up time in average among 224, 166, and 132 participants in olive oil, nuts, and control group, respectively, there are 35 cases of incident dementia (twelve in EVOO group; six in nuts group; seventeen in control group). Number needed to treat (NNT) is 13.29 for group with MD and additional EVOO treatment (ARR = 7.5% [95%CI 1.09% - 13.95%]). On the other hand, NNT is 10.79 for group with MD and additional nuts treatment (ARR = 9.2% [95%CI 2.88% - 15.65%]).

Discussion

This evidence based case report appraised a meta-analysis including RCTs and cohort studies that with at least one-year of follow up. In addition, recent RCTs were also reviewed. All of the articles provided high level of evidence. In general, MD is beneficial in elderly.[9-11]

As seen in the RCT by Valls-Pedret et al,[10] no dementia cases were documented in all participants following 4.1-year median follow up. On the other hand, after 6.5-year mean follow up in study conducted by Martínez-Lapiscina et al,[11] there were documented dementia cases. The absolute benefit of MD treatment with one L of EVOO is 7.5% reduction in dementia rate, whereas dementia rate is reduced by 9.2% in the group receiving MD treatment with nuts compared to the control group. Earlier RCT result published by Valls-Pedret et al,[10] showed 5.3% absolute reduction in rate of MCI in the cohort receiving MD with nuts (p=0.28). There were also conflicting evidence regarding MMSE results in the experimental groups. The improvement was not statistically significant in the experiment groups in the 4.1-year follow up trial,[10] but MMSE results were significantly better in the experiment groups in the 6.5-year follow up trial.[11] Follow-up length variation could be a crucial factor leading to difference in risk estimates. RCTs with longer follow up duration are required for the estimation of neuroprotective effect of MD.[9] In other words, longer period of adoption of MD in daily life is important to obtain significant benefit.

Memory composite improvement was seen in the nuts group (p<0.01), and frontal and global cognitive function composites were significantly improved in the cohort receiving MD with EVOO (p<0.01).[10] In general, beneficial effect of MD is 30% decrease in cardiovascular disease risk[12], including coronary artery disease, hypertension and dyslipidaemia.[9] The damaging oxidative processes in the brain may lead to neurodegeneration.[9,10] The impact on cognition may come from the high level of antioxidants and anti-inflammatory agents in the MD. Nuts and EVOO are rich in phenolic compounds to counteract the oxidative processes. Polyphenols modulate neuronal signalling, enhance cerebrovascular blood flow, as well as increase neurotrophic factor production and neurogenesis stimulation.[10] In the appraised clinical trial including participants with either diabetes mellitus or three or more major cardiovascular risk factors, MD also had beneficial effect.[11] This may be in part due to antidiabetic effect of polyphenols, despite the association between diabetes and cognitive decline.[10] There was an established link between MD and significant decrease in serum insulin level, plasma glucose level, and insulin resistance.[9]

Neuroprotective effect of MD however relied on the adherence to the diet. Singh et al[9] in 2014 showed that the significant difference only occurs in studies with highest diet adherence, but not in those with lower adherence.[9] There is association between higher adherence to MD and lower interleukin levels, as well as C-reactive protein.[10]

The use of diet adherence screener was designed for rapid assessment of compliance to MD pattern in spite of lacking measures for cooking method, frequency of domestic food intake and socialisation at meals. The traditional MD has several culinary and psycho-social elements, although some of these elements escaped current researcher's attention. MD traditionally involved domestic cooking method and home-grown produce. High moisture and lower temperature are included in the traditional slow cooking methods utilised in MD. Main meals were consumed by sitting around the table and snack between meals was uncommon. There was regular consumption of traditional culinary combinations and foods including Greek yoghurt and olives, as well as the combination of vegetables drizzled with EVOO and lemon juice. Short nap then followed the

main midday meal. Mediterranean people also traditionally practised fasting or food restriction.[12]

The traditional MD elements may have positive impact on health, for example the decrease in advanced glycation end products (AGEs) production pertaining to slow cooking methods. Slow cooking of the vegetables increase bioavailability of phytonutrients from the broken down plant cell walls. Moreover, EVOO in the diet is also beneficial for fat soluble phytonutrient consumption.[12] Beneficial effect of MD may come from the individual dietary components.[9] The MD is low in meat, eggs, animal fats and dairy products. On the other hand, the diet is high in unprocessed plant food and moderate in fish/shellfish and wine, see Figure 2.[12,13] Social connectedness is also a part of the traditional diet, which is important for health. Following main meals, infrequent snack may also lower the tendency to be obese. In Greek population, siesta after the midday meal has been associated with reduced coronary death. Siesta is also associated with reduction in blood pressure.[12]

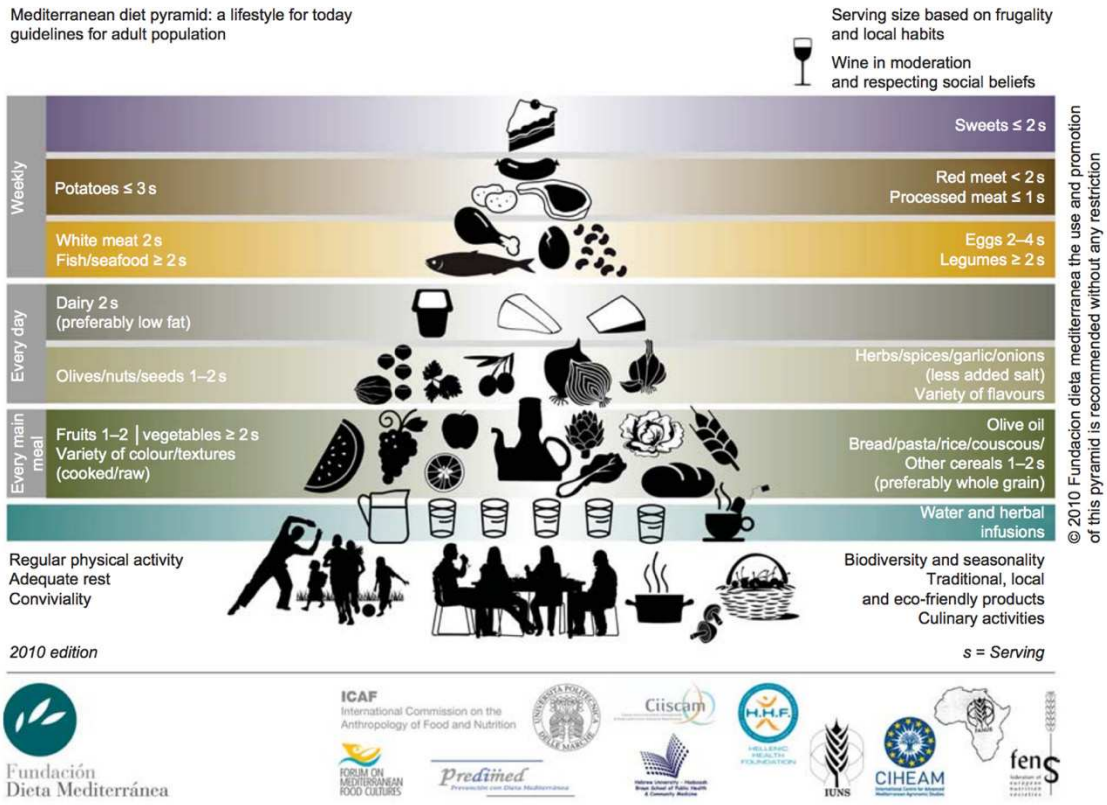

Figure 2. Mediterranean diet pyramid. Reproduced from Bach-Faig et al[13] who encouraged unrestricted image utilisation

Unfortunately, in places with different diet culture, difficulties may be found regarding the adoption of MD. Interventions are required to overcome the barriers. Tips for eating out with recommended healthier restaurants and menu options can be given in cases of high availability of fast food, but low availability of MD food. Education should be given in view of limited knowledge in the society. There are common misperceptions pertaining to the diet, for example the notion about fattening effect of EVOO and nuts consumption. In fact, current evidence proved that MD components do not promote adiposity. Hence, education based on evidence-based information is needed to promote the replacement of saturated fat with polyunsaturated and monounsaturated fats. Moreover, different labelling, stepwise small changes, tasting session of the diet may be needed in the presence of cultural barrier.[14]

Concern about the diet regimen budget may be overcome by giving low cost meal recipe suggestion.[14] In Indonesia, modifiable and affordable food includes a type of traditional salad with peanut sauce-based dressing, namely gado-

gado. This food contains 137 kcals for every 100 g portion.[15] Consumption of this dish is in accordance with the MD, which includes plant-based foods situated at the base of the food pyramid. Gado-gado generally includes blanched vegetables, such as spinach, water spinach, bean sprouts, green bean, bitter melon and chayote. The vegetables are commonly served with tofu, tempeh, pestle-ground peanut sauce, with the choice of either rice cakes or steamed rice. Small changes in the food may include modification of gado-gado involving slow-cooking method of the vegetables, addition of olive oil, and change from rice cake to whole grain brown rice. Whole grain is the preferable type of cereals in the diet due to the possible loss of valuable nutrients and fibres during food processing.[13]

As a majority of Indonesian population cannot condone with alcohol intake, there may be difficulties pertaining to regular alcohol consumption in MD. The conclusion of Global Burden of Disease study utilizing data from 195 countries was that the level of alcohol consumption in order to minimise health loss is zero. The higher the amount of alcohol consumed, thus the higher the risk of all-cause mortality.[16] Hence, it is probably acceptable not to include all MD components completely. Moreover, based on MD scale used for adherence assessment,[17] a participant only lost one from total nine points by not following ethanol consumption. By obeying other rules in the diet and only excluding alcohol from the diet simultaneously, an individual dietary regimen is still in accordance with the high adherence type of MD.

By introducing and applying MD in cognitively normal elderly in low- and middle-income countries with current trend of higher prevalence of dementia, the dementia rate can be reduced. Overall, without disrespecting religious and social beliefs, much attention should be paid to the adherence level of the adopted dietary regimen to MD due to the all-or-none neuroprotective effect of the diet.

As there are still some limitations in the included studies, future RCTs should have longer follow-up time and include statistical significance level of the difference in dementia rate when comparing the experiment and control group. As adoption of MD in non-mediterranean countries is of great interest, regional RCTs should be conducted for population-specific data.

Conclusions

Long-term MD may be beneficial for reduction in dementia rate. Study with shorter follow-up period however did not show difference in dementia incidence in experiment and control groups. In addition, neuroprotective effect of MD is achievable only in case of highest adherence to the diet.

In view of possible refusal to follow MD in elderly people, healthier restaurant and food recommendations, evidence-based education, and recipe suggestion are important. Different labelling, tasting session, and small changes of the diet can be taken into consideration. In Indonesia, small alterations may include slow cooking method of vegetable, addition of olive oil, and change from rice cake to whole grain brown rice to serve gado-gado.

Future RCTs should have longer follow-up time and include statistical significance level of the difference in dementia rate when comparing the experiment and control group. Regional RCTs should also be conducted for population-specific data in non-mediterranean countries.

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