Review Article

Low all-cause mortality despite high cardiovascular risk in elderly Greek-born Australians: attenuating potential of diet?

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Elderly Greek-born Australians (GA) consistently show lower rates of all-cause and CVD mortality compared with Australian-born. Paradoxically, however, this is in spite of a higher prevalence of CVD risk factors. This paper reviews the findings from the Food Habits in Later Life (FHILL) study, other studies on Greek migrants to Australia and clinical studies investigating dietary mechanisms which may explain the "morbidity mortality paradox". The FHILL study collected data between 1988 and 1991 on diet, health and psycho-social variables on 818 people aged 70 and over from Sweden, Greece, Australia (Greeks and Anglo-Celts), Japan and were followed up for 5-7 years to determine survival status. The FHILL study was the first to develop a score which captured the key features of a traditional plant-based Mediterranean diet pattern (MDPS). A higher score improved overall survival in both Greek and non-Greek elderly reducing the risk of death by 50% after 5-7 years. Of the 5 cohorts studied, elderly GA had the lowest risk of death, even though they had the highest rates of obesity and other CVD risk factors (developed in the early years of migration with the introduction of energy dense foods). GA appeared to be "getting away" with these CVD risk factors because of their continued adherence in old age to a Mediterranean diet, especially legumes. We propose that the Mediterranean diet may, in part, be operating to reduce the risk of death and attenuate established CVD risk factors in GA by beneficially altering the gut microbiome and its metabolites.

Key Words: morbidity mortality paradox, all-cause mortality, CVD risk factors, Mediterranean diet, microbiome

INTRODUCTION

Why the interest in Greek-born Australians: low mortality but high morbidity

The interest in first generation Greek-born Australians (GA) began in the 1980s when mortality data indicated they were the second longest lived population in the world after the Japanese migrants in Hawaii. Greek migrants to Australia were even living longer than their counterparts in Greece.[1] In 2011 GA continue to have one of the lowest levels of all-cause mortality mainly due to about 35% lower mortality from cardiovascular disease (CVD) and cancer compared with the Australian-born (see Table 1).[2] However, this is in spite of 2-3 times higher prevalence of obesity, diabetes, hyperlipidaemia, hypertension, inactivity and smoking (men only) in 1990 and 1995 (see Figure 1).[3-5]

In 1993, Bennet first reported that the low rates of CVD mortality of GA were insufficiently explained by the traditional risk factors from the 1980, 1983 and 1989 Risk Factor Prevalence Surveys.[6] In 1996, Kouris-Blazos et al confirmed Bennett's observation or "morbidity mortality paradox" when the food habits, health and psycho-social variables were studied in elderly GA and Anglo-Celtic Australians (ACA) between 1990-1992.[7] Mortality data were also collected in 1996 and paradoxically mortality of the slimmer ACA (only 10% obese) was 80% higher than the more overweight GA (30-46% obese).[8] It was estimated that 38% of this excess mortality of elderly ACA over that of GA could be explained in terms of their different dietary habits, essentially stronger adherence to a Mediterranean dietary pattern by GA and poor adherence by ACA. In 1997 and 2005, Itsiopoulos and coworkers also reported a "Greek Paradox" or apparent dis-association between mortality from CVD and higher rates of risk factors (especially diabetes and obesity) in a cohort of 453 Greek-born and Australian-born middle aged men and women recruited from the Melbourne Collaborative Cohort Study, a prospective cohort study of over 41,500 people.[4,5]

A qualitative retrospective study by Kouris-Blazos on 189 elderly GA in 1992 identified several dietary changes that may have contributed to the current high prevalence of obesity and CVD risk factors.[3,9] GA reported consuming significantly more fatty red meat (mostly barbequed), yellow cheese, milk, butter, margarine, vegetable oil, sugar dense foods and white bread in the first 10-20 years

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Table 1. Standardised mortality ratios† of overseas-born Australians compared with Australian-born: persistent low mortality from heart disease, stroke and cancer of Greek-born Australians in 2001[2]

Country of birth	Colorectal cancer	Lung cancer	Diabetes	Coronary heart disease	Cerebro-vascular disease	Influenza & pneumonia	All causes of death
China	0.74*	1.00	0.79*	0.49*	0.86	0.57*	0.65*
Croatia	0.96	0.83	1.25	0.77*	0.89	0.75	0.81*
Germany	0.86	1.09	1.38*	0.99	0.95	0.60*	0.94*
Greece	0.83*	0.72*	1.28*	0.76*	0.69*	0.75*	0.77*
India	0.51*	0.67*	1.78*	0.96	0.77*	0.77	0.75*
Italy	0.92	0.91*	1.67*	0.84*	0.76*	0.82*	0.87*
Lebanon	0.65*	0.83	2.18*	0.99	0.91	0.84	0.86*
Malaysia	0.55*	0.56*	1.09	0.58*	0.76*	0.75	0.67*
Netherlands	0.79*	1.32*	1.09	0.93*	0.88*	0.93	0.93*
New Zealand	1.06	0.95	0.78*	1.03	1.02	1.08	0.98
Philippines	0.68*	0.72*	0.96	0.48*	0.95	0.6	0.60*
Poland	0.99	1.15	1.36*	1.16*	0.97	1.02	1.01
South Africa	0.72	0.73	0.67	0.74*	0.85	0.90	0.81*
UK & Ireland	0.88*	1.3*	0.92*	1.01	0.94*	1.13*	1.01*
Vietnam	0.43*	0.69*	1.28	0.36*	0.82*	0.40*	0.59*
All overseas	0.87*	1.07*	1.24*	0.96*	0.91	0.96*	0.93*

*Statistically significant difference from Australian-born population.
†The standardised mortality ratio is a measure of death from a specific condition in the overseas-born population relative to the Australian born population. If the ratio is 1.00 this means the overseas-born would have the same mortality rate as the Australian-born. Ratios greater than 1.00 indicate a greater mortality rate in the overseas-born, and those below 1.00 indicate a lower mortality rate. Data are age-standardised to the Australian population as at 30 June 2001. Source: AIHW National Mortality Database, ABS 2012.[2]

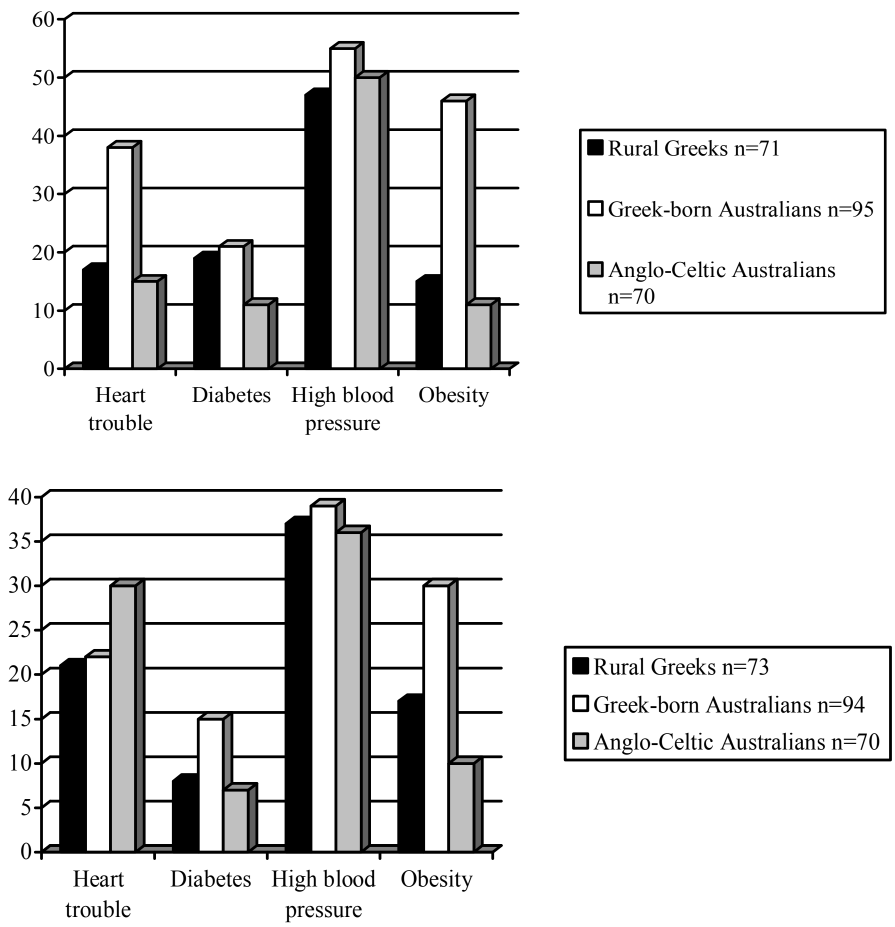

Figure 1. Percentage prevalence of heart trouble, diabetes, hypertension and obesity BMI>30 kg/m^2 in elderly rural Greeks, Greek-born Australians and Anglo-Celtic Australians aged 70 and over in the FHILL study. Source: Kouris-Blazos et al 1996[7].

of migration (1950-1970) in comparison to amounts they consumed in Greece prior to migration. In Greece, these foods were eaten infrequently (less than once a week) or not at all. However, there was a prevailing belief that these foods were a sign of being prosperous in their new country which to some extent justified their consumption.

The rapid increase in consumption of these energy dense foods would have contributed to the sharp increase in obesity and the development of CVD risk factors. Fortunately, they reported continuing to consume (into old age) many traditional foods like legumes, wild greens, tomatoes, garlic, onion and other vegetables, fruits, fish and seafood, olive oil, olives, nuts, fetta cheese, yoghurt, wine and herbs. The continued intake of such putatively protective foods may have, to some extent, off-set the adverse effects of these emerging CVD risk factors. Interestingly, 30% of the subjects reported fasting from animal foods twice a week for religious reasons (which helped them adhere to a more plant-based traditional diet) and 70% reported having a vegetable garden at home. It is unknown what impact these may have on the health and longevity of GA. The qualitative study also revealed that many subjects returned to a more traditional Greek diet (i.e less animal food) from about age 60, coinciding with retirement which enabled them to keep a home garden and consume more traditional vegetable-based dishes. This explains why 80% of the sample studied in 1992 (aged over 70) was found to be adhering to a more traditional Greek dietary pattern. This, in turn, appeared to be reducing the risk of premature death (see below).

MEDITERRANEAN DIET IN THE 1960S

The Mediterranean diet was first publicized in the 1960s as a health protecting diet by Ancel Keys and colleagues following the findings of the Seven Country Study.[10] The Seven Country Study was formally started in 1958 in former Yugoslavia, and included a total of 12,763 men, 40-59 years of age, enrolled as 16 cohorts, in seven countries. One cohort in the United States, two cohorts in Finland, one in the Netherlands, three in Italy, five in the former Yugoslavia (two in Croatia, and three in Serbia), two in Greece (Crete, Corfu), and two in Japan. At the 15 year follow-up the incidence of CHD mortality in Crete was one-thirtieth the incidence in Finland. The high monounsaturated to saturated fat ratio, resulting from a high intake of olive oil and low intake of animal fats, in the diet of Cretan Greek men was associated with lower serum cholesterol and lower mortality from CHD and cancer. Paradoxically, total fat intake was not linked to CHD.[11] Keys concluded that there was something special about the Cretan Mediterranean diet because of the long life and good health of the Cretan men. As a result of the findings of the Seven Country Study, the Cretan diet has become the archetypal Mediterranean diet. The food intake of the Cretan men in the 1960s can be summarised as follows (adapted from Kromhout et al[12]):

1. At least 6 slices of stone-ground wholemeal sourdough bread.
2. At least 2 fruits per day.
3. At least 2 cups vegetables per day (especially wild greens and many dishes cooked in a tomato salsa with onions, garlic, herbs).
4. Meat (mainly sheep/goat) once a week or less (mainly casseroled/boiled).
5. Fish/seafood once a week or less (depending upon proximity to the sea).
6. Legumes 2-3 times a week (in place of meat).
7. Nuts at least 3 times a week, olives daily, about 3 eggs a week.
8. Sheep/goat's cheese or yoghurt (2-3 times a week or more if available); milk was reserved for children.
9. Extra virgin olive oil more than 4 tablespoons per day.
10. Wine 100-200 mL per day, herbal teas (sage, sideritis) and ground coffee daily.
11. Herbs (mainly oregano), some spices (mainly cinnamon).

FIRST MEDITERRANEAN DIET PATTERN SCORE (MDPS)

The Seven Country Study and other epidemiological studies at that time had not properly documented an association between precisely defined food patterns and overall survival. Furthermore, the association between the Mediterranean diet and the mortality advantage of Mediterranean people may have been caused by traditional foods and cuisines specific to these cultures. It was not known whether a Mediterranean-style dietary pattern could confer the same mortality advantage in non-Mediterranean populations. Therefore, in 1995 a simple score was developed for the first time to assess adherence to the Mediterranean food pattern focussing on broad food groups but not reflecting cooking methods or aspects of the cuisine. The score was derived from the traditional Cretan diet from the Seven Countries Study. This Mediterranean Diet Pattern Score (MDPS) ranging from 0-8 was developed by Trichopoulou, Kouris-Blazos and Wahlqvist and was applied to data collected for the Food Habits in Later Life study (FHILL) (see below).[13]

The Mediterranean Diet Pattern Score (MDPS) was characterised by the following 8 food components (based on median daily intake in g/day, energy adjusted to 2500 kcal for men and 2000 kcal for women), resulting in a score ranging from 0-8:

1. High intake of vegetables (score 1 if intake>median; score 0 if <median).
2. High intake of legumes (score of 1 if intake>median; score 0 if <median).
3. High intake of fruit/nuts (score of 1 if intake>median; score 0 if <median).
4. High intake of cereals (including bread/potatoes) (score of 1 if intake>median; score 0 if <median).
5. High monounsaturated: saturated fat ratio (score of 1 if intake>median; score 0 if <median).
6. Low intake of dairy (score of 0 if intake>median; score 1 if <median).
7. Low intake of meat/fish (score of 0 if intake>median; score 1 if <median).
8. Moderate ethanol (score of 0 if intake >25 g women >50 g men; score 1 if <25 g women <50 g men).

The design of the score favoured a more plant based (or vegetarian) diet for which there was considerable evidence showing reduced mortality and morbidity from chronic diseases (in contrast to a more animal-based diet).[14] It was hypothesised that a more varied diet (a higher score) that favoured plant foods would have a beneficial health and survival effect and would resemble more closely to the traditional Cretan Mediterranean diet of the 1960s studied by Ancel Keys. A score $\geq$4 was considered to be strongly adherent to a Mediterranean diet pattern and therefore associated with longevity and low CVD mortality. In contrast, a score below 4 would be less representative of this diet and therefore less healthy. These considerations are based on both epidemiological and biological evidence.[15,16]

Values of 0 or 1 were assigned to each component by using the gender and cohort specific median intakes in g/day in the studied population as cut-offs. Food quantities in g/day were adjusted using daily intakes of 2500 kcal for men and 2000 kcal for women. A value of 1 was assigned to consumption (above the median) of food groups with a presumably beneficial effect (i.e vegetables, legumes, fruit and nuts, cereals, monounsaturated: saturated fat ratio). A value of 0 was assigned to consumption (above the median) of food groups with a presumably less beneficial effect (i.e meat, fish, dairy). For ethanol, a value of 1 was assigned to men who consumed quantities from 10 g (or one unit) a day to less than 50 g (or five units) a day and a value of 0 otherwise; the corresponding cut-offs for women were 5 g a day and 25 g a day. The MDPS values range from 0 (minimal conformity to the traditional Mediterranean diet pattern) to 8 (maximal conformity to the traditional Mediterranean diet pattern).

Elderly Greek-born Australians (GA) living longer than Greeks in Greece (GG)

The Food Habits in Later Life (FHILL) was a cross-cultural study conducted under the auspices of the International Union of Nutritional Sciences (IUNS) and the World Health Organisation (WHO) by Professor Wahlqvist and Dr Kouris-Blazos. This study determined to what extent health, social and psycho-social variables, especially food intake, collectively predicted survival amongst long-lived cultures. A total of 818 participants aged 70 years and over, were recruited from five IUNS centres: Japan (n=89), Sweden (n=217), Greece (rural areas n=182) and Australia (Greek-born n=189 and Anglo-Celtic Australians n=141). Between 1989-1991 cross-sectional data were collected using validated questionnaires, along with blood tests and anthropometry. Mortality data were collected after 5 to 7 years.[17] Based on up to seven years survival data, it was found that being an elderly Greek in Australia conferred the lowest overall mortality risk and being an elderly Greek in rural Greece conferred the highest mortality risk. Anglo-Celtic Australians had the 2nd highest overall mortality followed by the Japanese and Swedes (see Figure 2).

First observational study showing benefits of the Mediterranean diet pattern and legumes on longevity in old age

In order to understand the effect of diet and psycho-social variables on mortality, Kouris-Blazos et al analysed the effect of the MDPS on survival in GG and GA.[8] It was found that both elderly GG (n=182)[13] (see Figure 3) and GA (n=189)[8] who adhered to the more plant-based Mediterranean dietary pattern (i.e had scores ≥4) had a 50% reduced risk of death after 5 years.

Interestingly, only 57% of elderly GG were adhering to a Mediterranean diet pattern compared with 81% of the elderly GA, which partly explained the 30% lower mortality in the latter. Furthermore, when the MDPS was applied to elderly ACA (n=141) there was also a 50% reduced risk of death in those that adhered to a Mediterranean diet pattern. Only 28% of ACA were found to have scores ≥4 which partly explained their 83% higher mortality than GA. It was calculated that 37% of this mortality was due to lack of adherence to a Mediterranean dietary pattern.[8]

Darmadi et al investigated the relative importance of the individual components of the MDPS using data from FHILL (n=785).[18] In this analysis, fish was separated from meat into its own group resulting in 9 food groups. Using Cox proportional hazard regression analysis it was found that a regular intake of legumes was the strongest predictor of mortality protection and therefore the most important food group for longevity, reducing risk of death by 8% for every 20 g consumed (p=0.02). A trend was observed for higher intake of fish and total monounsaturated fats and reduced mortality.

Trichopoulou et al also investigated the relative importance of the individual components of the MDPS using data from the Greek cohort (n=23,349) of the EPIC study (European Prospective Investigation into Cancer and Nutrition).[19] In this analysis, fish was also separated from meat into its own group resulting in 9 food groups. After a mean follow-up of 8.5 years, participants with scores ≥4 had a statistically significant reduction in total mortality by 28%. The contributions of the individual food components to this association were moderate ethanol consumption 23.5%, low consumption of meat 16.6%,

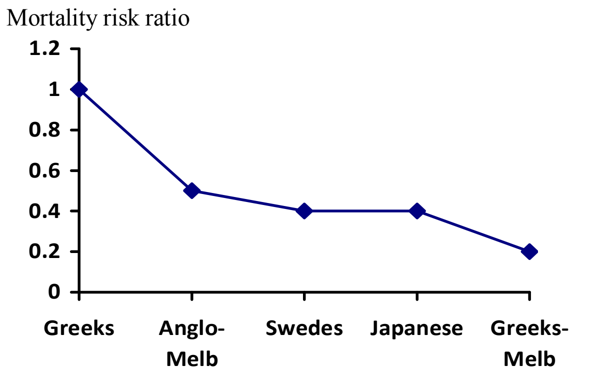

Figure 2. Mortality risk ratio after 5 years follow-up for elderly cohorts; Greeks in rural Greece (n=182), Anglo-Celts in Melbourne (n=141), Swedes (n=217), Japanese (n=89) and Greeks in Melbourne (n=189), (95% CI, Cox Proportional Hazards Regression) in the FHILL study. Source: Kouris-Blazos.[67]

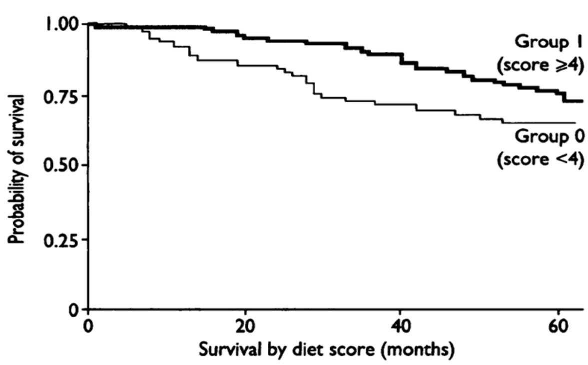

Figure 3. Elderly Greeks in Greece aged 70 and over (n=182) have lower mortality after 5 years if they follow a more traditional Greek dietary pattern (score ≥4) (Kaplan Meier survival curves). Source: Trichopoulou et al.[13]

high vegetable consumption 16.2%, high fruit and nut consumption 11.2%, high monounsaturated to saturated fat ratio 10.6% and high legume consumption 9.7%. The contribution of high cereal and low dairy consumption were minimal whereas (surprisingly) high fish consumption was associated with a non-significant increase in mortality. The authors concluded that moderate ethanol intake, low meat intake, high monounsaturated/low saturated fat intake and high intake of plant foods were driving the association of high Mediterranean diet score with low mortality.

How important is the Mediterranean dietary pattern for longevity compared to other psycho-social variables?

To determine how important the Mediterranean dietary pattern was relative to other psycho-social variables ten potential predictors of survival were analysed in the FHILL study: 1) Mediterranean diet pattern score 2) memory score 3) general health score 4) activities of daily living (ADL) score 5) exercise score 6) social activity score 7) social networks score 8) wellbeing score 9) smoking 10) gender. This analysis revealed that the Mediterranean diet pattern was more important than most of the psycho-social variables for survival (13% reduced risk of death), except for smoking (67% increased risk of death), being male (63% increased risk of death) and having a poor memory (22% reduced risk of death).[17]

HAS THE MEDITERRANEAN DIET PATTERN SCORE (MDPS) BEEN USED IN OTHER OBSERVATIONAL STUDIES?

The MDPS developed in 1995 for the FHILL study (or variants of it) has facilitated researchers around the world to explore the health benefits of the Mediterranean diet resulting in an exponential number of studies. In a review paper by Sofi et al this fact was highlighted as follows: "The first study that showed a possible effect of the Mediterranean diet in reducing the risk of death from any cause is that one by Trichopoulou et al performed in 1995.[13] This pioneering study assessed for the first time adherence to the Mediterranean diet by using a score."[20]

MDPS, all-cause mortality, CVD mortality and CVD events

A higher MDPS (or greater adherence to a Mediterranean dietary pattern) has consistently been shown to reduce overall mortality and mortality from CVD. The most relevant since the FHILL study, is the EPIC study in Greece and Denmark. In Greece (n=22,000), a higher MDPS showed 25% reduced risk of death from all causes with every 2 point increase (HR: 0.75, 95% CI 0.64-0.87).[21] In Denmark (n=202) a one unit increase in the MDPS predicted a 21% (95% confidence interval 2%-36%) reduction in mortality.[22] Interestingly, Danish subjects with high diet scores (≥4) also had significantly higher plasma carotene levels than those with a low score and plasma carotene was negatively associated with mortality. A 7% reduced risk of death from all causes has also been reported for all cohorts in the EPIC study (n=74,607) with a 2 point increment in the MDPS.[23]

A meta-analysis by Sofi et al summarised the results of nine cohort studies (n=+500,000) that evaluated the relation between adherence to the Mediterranean diet using the MDPS and overall mortality, mortality and incidence of CVD and cancer, and the incidence of Alzheimer's and Parkinson's disease.[24] An inverse association was noted in all these studies. An increase of 2 points in the score (ranging from 0 to 9) resulted in an 8-9% reduction in overall mortality and incidence and/or mortality from heart disease and strokes (RR 0.91, 95% confidence interval 0.89 to 0.94, p<0.0001). Associations were stronger in studies done in Mediterranean countries[21,25,26] compared with studies done in Western European countries and Sweden,[27] although no statistically significant heterogeneity existed.[24,28] There have been seven new cohort studies investigating CVD (fatal or non-fatal clinical event) and MDPS, since the Sofi et al meta-analysis. Gonzalez and Bes-Rastrollo have updated the meta-analysis with these new studies.[29] A two-point increase in adherence to the MDPS was associated with a significant 13% relative reduction in the incidence of CVD events (pooled risk ratio: 0.87 CI: 0.85-0.9) with no evidence of heterogeneity. These results support an inverse linear association between the Mediterranean diet and CVD and are consistent with the previous pooled estimate reported by Sofi et al.[24]

In two large Spanish cohorts (EPIC study) a higher MDPS was linked to a 40% to 59% reduction in CVD events.[30,31] Similarly, in a large Greek cohort in the EPIC study (n=22,000), for every 2 point increase in the score there was a 33% reduction in CVD mortality and a 26% reduction in the onset of CVD.[21] A similar conclusion was also reached by the HALE, SENECA and FINE studies (multicentre studies from Mediterranean and non-Mediterranean countries on over 2000 people aged over 70)[32] as well as two large studies in the US.[33,34] In the EPIC study (n=2671 from 9 European countries) a higher MDPS was also found to be associated with the prevention of heart attacks in patients with a previous diagnosis of myocardial infarction i.e secondary prevention; an increase of 2 units in the MDPS was associated with an 18% reduction in CVD mortality.[26,35]

MDPS and other health problems

A higher MDPS has also been associated with a lower risk of developing Alzheimer's disease,[24,28] Parkinson's disease,[24,36] diabetes mellitus,[37,38] and cancer.[24,27,28] In the Greek cohort of the EPIC study (n=22,000) a higher MDPS resulted in a reduction of death caused by cancer by 24% (RR: 0.76, 95% CI 0.56-0.98).[21] An analysis of the global population of the EPIC study (n=485,044) followed for about 9 years, showed that a higher MDPS was associated with a reduction of 33% in the risk of gastric cancer.[39] Overall, studies have not found the Mediterranean diet high in olive oil to cause weight gain – quite the reverse.[40] A higher MDPS in the EPIC study, which included a cohort of 497,308 people aged 25-70 years from 10 European countries, was associated with a significantly lower BMI and waist circumference.[41] In the ATTICA study in Greece, a higher score was associated with a reduction in the risk of being obese by 51% in over 3000 subjects.[42] In a Spanish study, an increase in the MDPS by 5 units resulted in a significantly lower risk of obesity in both men and women (n=3162).[43]

ARE THERE ANY MEDITERRANEAN DIET INTERVENTION STUDIES?

The first randomised Mediterranean diet intervention study was conducted in the 1990s in France and was known as the "The Lyon Diet Heart Study".[44] This was the first randomized trial to demonstrate the efficacy of the Mediterranean diet in the secondary prevention of CVD, with a dramatic 70% reduction in overall mortality and cardiac event rates (which were independent of classic CVD risk factors), compared with those on a conventional low fat diet.

Another, much larger, randomised intervention study was conducted in Spain, the Prevention con Dieta MEDiterranea trial (PREDIMED), on 7,447 high risk participants (with no history of CVD).[45] This was the first randomized trial to demonstrate the efficacy of the Mediterranean diet in the primary prevention of CVD with a 30% reduced risk in the incidence of developing an initial major CVD event. A meta-analysis combining these two trials showed a relative 38% reduction in the risk of CVD after intervention with a Mediterranean diet.[29]

WHAT ARE THE POSSIBLE BIOCHEMICAL AND PHYSIOLOGICAL MECHANISMS RESPONSIBLE FOR THE HEALTH BENEFITS OF THE MEDITERRANEAN DIET?

The underlying mechanisms by which the Mediterranean diet exerts its beneficial functions are far from being totally understood. Current knowledge suggests that diets operate beyond the conventional CVD risk factors like blood cholesterol, blood pressure or body weight. It is now thought that underlying mechanisms involve oxidative stress, coagulation, endothelial function and inflammation,[46] partly driven by a disturbed gut microbiome.[47] Abberant gut microbiota profiles have been associated with obesity, diabetes, CVD, fatty liver, certain cancers and various autoimmune disease. Also, the flux of metabolites derived from gut microbial metabolism of choline, phosphatidyl choline and L-carnitine has been shown to contribute directly to CVD pathology, providing one explanation for increased disease risk of eating too many animal foods, especially red meat.[48] The traditional Mediterranean diet is low in animal foods, especially red meat.

Conventional CVD risk factors

With respect to conventional CVD risk factors, Mediterranean diets have been shown to lower blood pressure, total cholesterol, LDL cholesterol, triglycerides, blood glucose, waist circumference and to raise HDL cholesterol.[49] Olive oil and monounsaturated fat rich diets have been shown to lower blood pressure.[50,51] Oxidation of LDL cholesterol is known to be a key factor in the development of atherosclerosis, promoting the formation of foam cells in the sub-endothelial space of the vascular wall. LDL resistance to oxidation is augmented when the Mediterranean diet rich in olive oil replaces diets rich in saturated fats. The phytochemicals present in extra virgin olive oil, especially the phenolic hydroxytyrosol, have not only been found to protect LDL cholesterol from oxidation, but also have anti-inflammatory action (by reducing NFKappa-6) and anti-clotting action (by reducing thromboxane B_2, fibrinogen).[46,52] Furthermore, the traditional Mediterranean diet is naturally high in antioxidants (with the potential to reduce LDL oxidation) due to the high content of plant-derived antioxidants from vegetables, fruits, nuts, legumes, herbs and olive oil. Lycopene, a carotenoid abundant in tomatoes and watermelon, is known to be a powerful antioxidant scavenger, hypolipidaemic agent and inhibitor of pro-inflammatory and pro-thrombotic factors.[53] Resveretrol, a natural antioxidant found in red wine, has been shown to reduce oxidation of LDL cholesterol in in-vitro studies.[54]

A healthy vascular endothelium is essential for the proper functioning of blood vessels (such as vasodilation and vasoconstriction) and for the regulation of inflammatory cells involved in atherogenesis. Meals rich in olive oil have a favourable effect on postprandial vasomotor function of the endothelium, enhancing vasodilatory capacity during this phase, compared to meals rich in animal fats.[54,87] Nuts, fish and vegetables, commonly consumed in the Mediterranean diet, have also been shown to improve endothelial function by promoting a lower proinflammatory, prooxidant environment.[55,87] Also, a study by Marin et al showed that people following a Mediterranean diet improve the regenerative capacity of the vascular endothelium.[56] Other mechanisms include improved cardiac rhythm and cardiac autonomic function, with a lower probability of developing atrial fibrillation; blood vessels (especially the carotids) also have a favourable thinner intima media thickness (a measure of atherosclerosis).[46,87]

Diets rich in fruits, vegetables, grains, fish, low fat dairy products and olive oil have been shown to prevent the redistribution of body fat from the periphery to the more deleterious visceral adipose tissue which has been linked to diabetes and hyperlipidaemia.[57,87] The Mediterranean diet has been shown to prevent the development of diabetes by more than 50%[58] and to improve the metabolic control of diabetes in a randomised clinical trial of Anglo-Celtic Australians (n=27) with diabetes, by decreasing glycated haemoglobin.[59] Closer adherence to a Mediterranean diet has been shown to reduce mortality in Greek and Italian-born Australians with diabetes in a prospective cohort study of 41,500 people in Melbourne, Australia.[60] Some of the underlying mechanisms include the improvement of insulin sensitivity and blood lipids, improvement in postprandial lipaemia, glucose homeostasis and pancreatic beta cell insulin secretion.[46,87]

Microbiome

The gut microbiome is emerging as an important contributor to human health and the development of chronic diseases. Over the last 10 years, there is evidence that chronic diseases may in fact have infective contributors.[61] This represents a paradigm shift in our thinking regarding the cause and treatment of many chronic diseases. The human gastrointestinal tract is host to a complex microbial ecosystem of hundreds of bacterial species also known as the gut microbiome. A diverse microbiome appears to play a crucial role in the development of a healthy gut and immune system, while disturbances (or reduction in diversity) have been associated with systemic inflammation and chronic diseases. Animal, and a limited number of human studies, have shown that diets high in animal protein, fat and sugar and low in fibre and unrefined carbohydrates are associated with reduced microbiota diversity, increased relative abundance of undesirable bacteria and their toxic metabolites, including the cardiotoxicant trimethylamine-N-oxide (TMAO).[48]

In contrast, beneficial bacteria, especially the bifidobacteria, have anti-inflammatory properties, improve gut wall barrier function and possess bile salt hydrolase activity which helps to reduce blood cholesterol levels.[48] Beneficial metabolites are produced when carbohydrates and fibres are fermented by the beneficial bacteria in the colon such as the short chain fatty acids (SCFA) acetate, propionate and butyrate. These SCFA are absorbed via the colonic wall into the blood stream and have been shown in animal studies to regulate gut hormone production (eg, incretin) involved in controlling satiety and food intake. They also stimulate the gut hormone glucagon-like peptide 2 involved in maintaining gut barrier function. This is a defence mechanism which can impede the uptake of inflammatory compounds (such as bacterial cell wall lipopolysaccharides or LPS) from the gut lumen that trigger low grade chronic inflammation or “metabolic endotoxaemia”. SCFA have also been shown to regulate adipocyte hormone production (eg, leptin) and to control inflammatory processes in adipose tissue. These processes are intimately involved in CVD risk and the way food energy is stored or utilised in the body controlling adiposity and thermogenesis.[48]

LPS is an inflammatory cell wall constituent of Gram-negative bacteria which can cross the gut barrier and enter the host blood, leading to stimulation of inflammatory cascade through Toll-like receptor-4 and NF-kB. In animal studies LPS has been shown to trigger low grade chronic systemic inflammation and subsequent metabolic syndrome, insulin resistance, body weight gain, atherosclerosis and endothelial dysfunction (Table 2).[47,48,62] Decimation of beneficial gut bacteria has been accompanied by translocation of bacterial cell wall LPS across the gut wall, either through increased permeability due to reduced tight junction control or carried with fat absorbed from the gut.[48]

During food digestion, a large number of plant food chemical constituents (also known as prebiotics), are not digested and absorbed in the small intestine, but reach the colon to be metabolised by the gut microbiota. Dietary prebiotics promote the establishment of “good” bacteria in the large bowel by providing “food” for their survival.

Table 2. Disease states and conditions that have been associated with altered gastrointestinal microbiota (adapted from Binns,[63] Cho & Blaser,[81] Tilg & Kaser[82])

Metabolic syndrome
Diabetes
Obesity
Cardiovascular disease
Liver disease
Chrohns disease and ulcerative colitis
Coeliac disease
Colon cancer
Irritable bowel syndrome
Rheumatoid arthritis
Allergy and asthma
Depression and anxiety

Also, consuming fermented foods (probiotics) high in beneficial Lactobacilli and Bifidobacteria can also contribute to a healthy microbiome. The good bacteria in the large bowel (Lactobacillus, Bifidobacterium, butyrate-producing Firmicutes and polysaccharide degrading Bacteroidetes) ferment prebiotics to produce beneficial metabolites (such as SCFA) which are absorbed into the blood stream and exert a beneficial health effect by modulating the immune and inflammatory responses of the host.[63] The metabolites also remain in the gut to promote and maintain bowel health (eg, reduced gut permeability) and function and absorption of minerals.

It has been known for a long time that prebiotics include carbohydrates and dietary fibre such as polysaccharides (eg, pectins, hemicelluloses, gums, inulin, and resistant starches), oligosaccharides (raffinose, stachyose, galacto-oligosaccharides, fructo-oligosaccharides), sugars (lactulose, non-absorbed lactose and fructose) and polyols (mannitol, xylitol, maltitol, isomalt). In animal studies the prebiotic oligofructose has been shown to reverse metabolic endotoxaemia by reducing gut permeability and LPS leakage into circulation via the gut hormone glucagon-like peptide 2. It was also found to induce gut hormones glucose dependent insulinotropic polypeptide and glucagon-like peptide 1 which resulted in improved glucose homeostasis (by improving insulin sensitivity), lipid metabolism and satiety (by reducing gastric emptying).[48]

However, recently it has also been demonstrated for other food constituents, particularly phytochemicals like polyphenols.[64] Up to 95% of plant polyphenols escape digestion in the upper gut and reach the colon where they are transformed by resident microbiota into biologically active intermediates which can act systemically. They also have the ability to inhibit certain gut bacteria and stimulate the growth of beneficial bacteria and to alter redox potential within the gut thereby reducing the absorption of oxidised cholesterol species.[48]

In contrast, protein fermentation by dysbiotic bacteria in the large bowel is considered more detrimental for human health as it results in the production of potentially toxic carcinogenic and cardiotoxic bacterial metabolites such as trimethylamine (TMA), TMAO, phenols and sulphides.[64] In a large clinical cohort, Wang et al showed that plasma concentrations of choline, TMAO and betaine, all metabolites of phosphatidyl choline (PC) metabolism, are predictive of CVD.[65] Foods rich in PC (or lecithin) include eggs, milk, liver, red meat, poultry, shellfish and fish. Choline and other trimethyl amine species (eg, betaine) are fermented by dysbiotic bacteria to form the gas TMA, which is absorbed and converted to TMAO in the liver. In animal studies by Wang et al choline and TMAO feeding induced atherosclerosis.[65] Koeth et al showed that the peptide carnitine (high in red meat and in lower amounts in pork, poultry, fish and milk) with a structure similar to that of choline, may also be converted to TMA by the gut microbiota and contribute to the increased CVD risk associated with high red meat consumption.[66]

HOW IS GA ESCAPING PREMATURE DEATH DESPITE A HIGH PREVALENCE OF CONVENTIONAL CVD RISK FACTORS?

As discussed earlier, first generation GA who came to

Australia from 1950 to 1970 continue to exhibit much lower mortality from heart disease and cancer despite a high prevalence of conventional CVD risk factors (established in the first 20 years in Australia due to the introduction of energy dense animal foods) such as diabetes, obesity, hyperlipidaemia, hypertension and self-reported heart disease. We don't currently fully understand the mechanisms by which this has occurred and more research is needed.[3-6,67-69] However, diet and lifestyle factors (such as gardening, siesta) have probably played a role. About 50% the sample spent 30 mins or more in their vegetable gardens, especially the men.[9] Gardening not only contributes to their physical activity levels but also exposes their skin to sunshine and production of vitamin D, both of which can have a favourable effect on CVD risk factors and mortality.[70,71] Also, about 40% of the sample had a nap daily.[9] The daily siesta has been reported to reduce the risk of coronary mortality.[72] However, it is suspected that continued adherence to a Mediterranean diet, especially in old age, has played a major role in off-setting these risk factors.

So what is driving adherence to the traditional Greek diet by elderly GA? Cultures that have a stable history of many generations have food habits, food beliefs and traditions (especially religious) compatible with survival of the group in a particular setting. Traditional food cultures have developed over thousands of years and have been tested, refined and distilled producing a repertory of foods and processes for preparing them, capable of sustaining life in specific environments. The elderly are custodians of these traditions and may feel the responsibility to practice and pass on these traditions and beliefs to the next generation.[73] Migration would only act to intensify this responsibility driving adherence to the traditional Greek diet. For example over 75% of the GA (n=189) expressed the belief that legumes should be consumed (in place of meat) at least twice a week (about 30% of the sample was doing this), that meat should be restricted, and that all religious fasts should be undertaken if possible and if health permits (i.e vegan eating twice a week and for at least 100 days of the year).[9] Such beliefs would prevent the uptake of the Western diet. Religious beliefs have been identified as preventing dietary acculturation to the mainstream diet in migrant populations.[74]

For example, Brazionis et al identified significantly higher blood carotenoid levels in GA aged 50-70 years (n=213) compared to ACA (n=214) which was correlated with a lower prevalence of diabetic retinopathy.[75-77] Traditional foods consumed by GA (such as leafy greens, figs, olive oil) have been found to be particularly high in carotenoids.[78] High blood carotenoids have also been associated with lower overall mortality in elderly Danes following a Mediterranean dietary pattern.[22] Epidemiological studies suggest that diets high in carotenoid-rich fruits and vegetables are associated with reduced risk of CVD and some cancers but it is unclear whether the biological effects of carotenoids in humans are related to their antioxidant activity or other non-antioxidant activities.[79]

Apart from having higher blood carotenoid levels, elderly GA may also have better endothelial function, less oxidative stress, thinner blood, less systemic inflammation, atherosclerosis and toxic bacterial metabolites (possibly due to a healthier more diverse gut microbiome) protecting them from premature death. Steinle et al investigated the effects of a Mediterranean diet on the composition of the gut microbiome and on fasting lipids in 9 men and women aged 50-65 with prediabetes.[80] After 2 weeks on this diet there was a significant decrease in triglycerides and LDL cholesterol by about 13% and a significant increase in the diversity of the gut bacteria by about 10%. Further studies are needed to identify which specific group of microbes is responsible for this increase in diversity and their associations with metabolic and inflammatory makers.

We propose that some of the health benefits observed with the Mediterranean diet are operating in part, through the gut microbiome. Increasing or maintaining gut microbial diversity through a varied plant based diet protects the gut microbiome against the dominance of pathogens or dysbiotic bacteria which in turn may be preventing and attenuating the progression of chronic diseases (see Table 2)[81-84] especially CVD, diabetes and fatty liver.[85] The plant-based Mediterranean diet consumed by GA is high in both probiotics and prebiotics with the potential to favourably influence the gut microbiome which in turn may reduce circulating endotoxins, LPS, and the development or progression of CVD risk factors. Furthermore the diet contains foods/herbs/spices high in polyphenols with antimicrobial and anti-inflammatory properties which may improve the gut microbiome, reduce gut permeability and systemic inflammation by reducing dysbiotic bacteria (Table 3).[48] High polyphenol intake, especially from stilbenes (eg, grapes) and lignans (eg, sesame, legumes),

Table 3. Components of the traditional Mediterranean diet and cuisine which may have a favourable impact on the gut microbiome

Probiotics
Fetta cheese, yoghurt, olives, trahana (fermented wheat and milk), sourdough bread
Prebiotics
Legumes, nuts, grains, vegetables (especially onions, garlic, wild greens, artichokes), fruits (especially grapes, citrus, pomegranate), olives, olive oil, coffee, herbs, spices, honey
Polyphenols
Olives, olive oil, sesame, clove, cinnamon, oregano, thyme, mint, sage, sideritis, chamomile, lemon, wine, spirits
Cuisine & lower levels of advanced glycation end products (AGEs)
More casseroles, soups and raw food and less roasts, grills and barbeques
Higher proportion of plant foods relative to animal foods
Fasting from red meat, white meat (including fish but not seafood), milk and milk products, eggs and olive oil (for religious reasons, 2 days a week and up to 200 days a year in total)

have been shown to reduce the risk of overall mortality in subjects taking part in the PREDIMED study.[89] This study also reported that consumption of olive oil, specifically the extra virgin variety rich in polyphenols, is associated with reduced risks of CVD and mortality in individuals at high risk of CVD.[90]

Restriction of animal foods by GA during religious fasts, may also have a beneficial effect on the gut microbiome and reduce potentially toxic bacterial metabolites and inflammation.[84] Furthermore the traditional Greek cuisine relies mainly on cooking methods that retain moisture such as casseroling and boiling and less on grilling, roasting and barbequing. The latter cooking methods can result in unfavourable advanced glycation end products (AGESs) that can adversely affect gut permeability[86] and potentially the microbiome and metabolic endotoxaemia.

Understanding the links between the microbiome, Mediterranean diet and human disease may provide prophylactic or therapeutic tools to improve human health. We have the opportunity to examine some of these questions, especially the impact of religious fasting and consumption of home grown produce, with the 150 elderly GA currently being studied as part of the Australian arm of the Mediterranean Island Study (MEDIS).[88] MEDIS is a cross-sectional study of elderly Greeks from Greek islands in Greece compared to Greeks from these islands living abroad without history of chronic disease. The aim of MEDIS is to evaluate the relationships between diet and psycho-social characteristics and the presence of various CVD risk factors. The Australian study will further investigate the Greek migrant paradox to better understand how CVD risk factors can be made “benign”.

AUTHOR DISCLOSURE

None.

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Review Article

Low all-cause mortality despite high cardiovascular risk in elderly Greek-born Australians: attenuating potential of diet?

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希腊出生的澳大利亚老年人群尽管心血管疾病风险高，但全死因死亡率低：是由于他们的膳食引起的吗？

与澳大利亚出生的老年人相比，希腊出生的澳大利亚老人全死因死亡率和心血管疾病死亡率一直都较低，然而，这与其心血管疾病风险因子的高发率相矛盾。本文综述了希腊人移民到澳大利亚后生活饮食习惯对后期生命的研究，其研究结果可能能够用膳食机制解释临床研究的“发病率死亡率悖论”。本课题收集了 1988-1991 年之间关于生活饮食习惯对后期生命的研究，包括来自瑞典、希腊、澳大利亚（希腊人和盎格鲁-凯尔特人）、日本的 818 名 70 岁及其以上老人饮食、健康和社会心理等参数资料，随访 5-7 年以确定其生存状态。该研究首次形成以得分来获得以传统植物为基础的地中海膳食模式的主要特征。较高的得分能够提高希腊老人和非希腊老人总的生存率，并使其 5-7 年后的死亡风险降低 50%。5 个队列研究中，希腊出生的澳大利亚老人死亡风险最低，尽管他们的肥胖和其它心血管疾病风险因子的发生率最高（在移民早期因高能量密度食物的摄入而形成的）。希腊出生的澳大利亚人似乎“摆脱了”心血管疾病风险因子，因为他们在年老时仍然坚持地中海膳食，尤其是豆类。我们认为地中海膳食可能能够通过改变希腊出生的澳大利亚人的肠道微生物及其代谢产物，部分降低其死亡风险并减弱已确定的心血管疾病风险因子。

关键词：发病率死亡率悖论、全死因死亡率、心血管疾病风险因子、地中海膳食、微生物