Longevity in elderly Greek Migrants to Australia may be Explained by Adherence to a Traditional Greek Mediterranean Diet?

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Between 1988 and 1991 data were collected on diet, health and lifestyle on 818 people aged 70 and over from countries/cultures experiencing longevity: Swedes, Greeks, Australians (Greeks and Anglo-Celts) and Japanese. This was known as the Food Habits in Later Life study (FHILL). Subjects from these 5 cohorts were followed up for 5–7 years to determine survival status and to examine the effect of diet and lifestyle variables on longevity. 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 (i.e greater adherence to this dietary pattern) 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, first generation elderly Greeks in Australia had the lowest risk of death, even though they had the highest rates of obesity and other cardiovascular disease (CVD) risk factors (developed in the early years of migration with the introduction of energy dense foods). This was called a "Greek migrant Morbidity Mortality Paradox". Greek migrants appeared to be "getting away" with these CVD risk factors because of their continued adherence to a Mediterranean diet, especially legumes. This paper reviews a) the findings from the FHILL study b) other studies on Greek migrants to Australia c) clinical studies investigating possible mechanisms. We propose that the Mediterranean diet may be operating to reduce the risk of death and attenuate established CVD risk factors by beneficially altering the gut microbiome.

Keywords: Mediterranean diet, legumes, elderly Greek Australian migrants, longevity, CVD risk factors, diabetes, obesity, Greek migrant morbidity mortality paradox, microbiome, probiotics, prebiotics, phytochemicals, inflammation.

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Why the interest in migrant Greek 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 in Hawaii. The Greek migrants were even living longer than their counterparts in Greece (Young, 1986). 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 (ABS, 2010) (see Table 1).

Table 1: Standardised mortality ratios(a) of overseas-born Australians compared to Australian-born: persistant low mortality from heart disease, stroke and cancer of Greek-born Australians in 2010 (ABS 2012)

| 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
(a) 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.

However, this is in spite of 2–3 times higher prevalence of obesity, diabetes, hypelip-idaemia, hypertension, inactivity and smoking (men only) in 1990 and 1995 (Kouris-Blazos et al., 1999b; Itsiopoulos et al., 1997, 2005) (see Figure 1).

Figure 1: Percentage prevalence of heart trouble, diabetes, hypertension and obesity BMI >30 (weight kg/height m2) in elderly rural Greeks, Greek-born Australians and Anglo-Celtic Australians aged 70 and over in the FHILL study (Source: Kouris-Blazos, 1999)
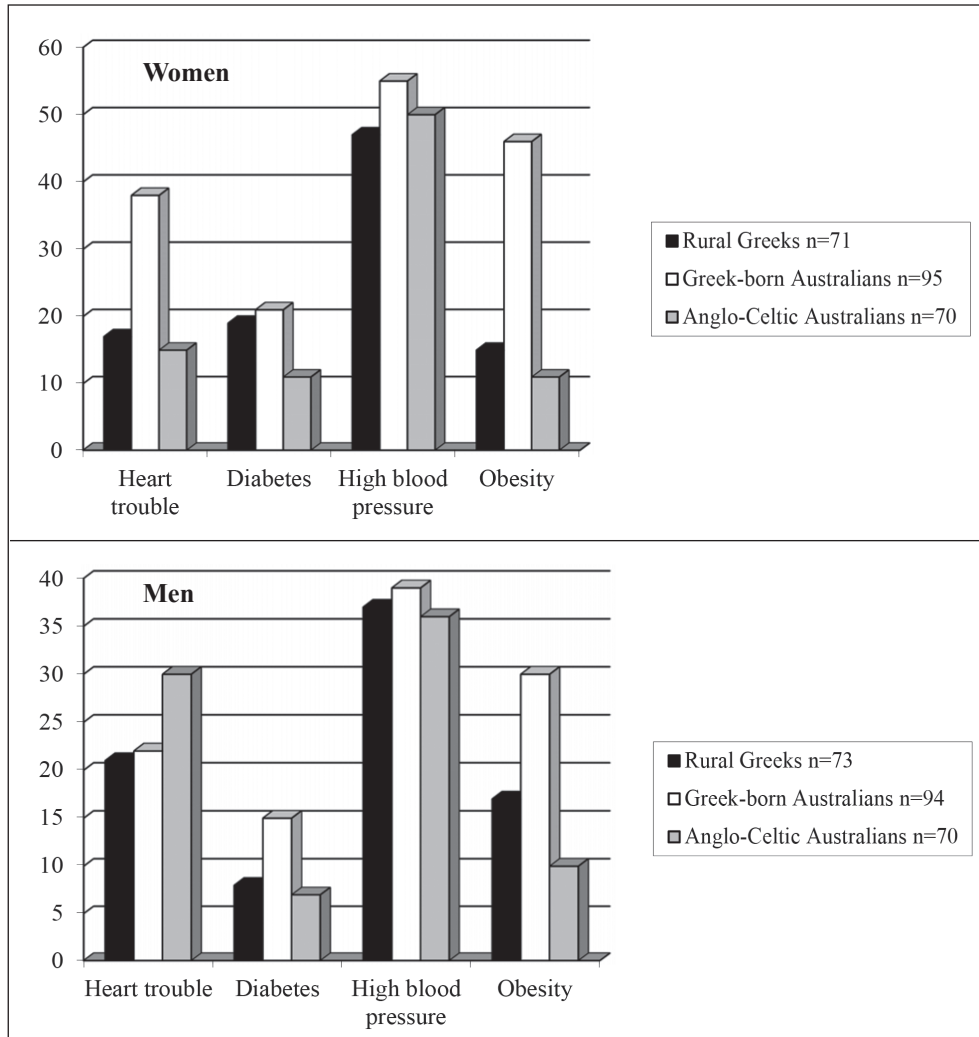
In 1993, Bennet first reported that the low rates of CVD mortality of GA were insufficiently explained by the traditional risk factors from the 1980, 1983 and 1989 Risk Factor Prevalence Surveys. In 1996, Kouris-Blazos et al., confirmed Bennett's observation or 'morbidity mortality paradox' when the food habits, health and lifestyle of elderly GA and Anglo-Celtic Australians (ACA) were studied between 1990–1992. Mortality data were also collected in 1996 and mortality of the slimmer ACA (only 10% obese) was 80% higher than the more overweight GA (30–46% obese) (Kouris-Blazos et al., 1999). 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 adherence to a Mediterranean dietary pattern by GAs and poor adherence by ACAs. In 1997 and 2005, Itsiopoulos and co-workers also reported a "Greek Paradox" or apparent disassociation 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.

A qualitative retrospective study by Kouris-Blazos (1994; 1999) on 189 elderly Greek Australians in 1992 identified several dietary changes that may have contributed to the current high prevalence of obesity and CVD risk factors. There was an over-whelming consensus amongst study subjects that they consumed 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 of migration (1950–1970) in comparison to amounts 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. Such a shift in food pattern and energy intake would have contributed to 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 would have, to some extent, off-set the adverse effects of these emerging CVD risk factors. Interest-ingly, 30% of the subjects reported fasting from animal foods twice a week for reli-gious reasons (which helped them adhere to a more plant-based traditional diet) and 70% reported having a vegetable garden at home. In addition, the qualitative study 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 death (see below).

Mediterranean diet in the 1960s

The Mediterranean diet was first publicised in the 1960s as a health protecting diet by The Seven Countries Study of Ancel Keys and colleagues (Keys, 1980). The Seven Countries Study was formally started in 1958 in former Yugoslavia. In total, 12,763 men, 40–59 years of age, were 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

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Crete was one-thirtieth the incidence in Finland. High intakes of monounsaturated fat from olive oil and low intakes of saturated fats from animal foods consumed by Cretan Greeks were associated with lower serum cholesterol and lower mortality from CHD and cancer. Paradoxically, total fat intake was not linked to CHD (Keys et al., 1984). 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 Countries Study, the Cretan diet has become the archetypal Mediterranean diet. The food intake of the Cretan men in the 1960s from The Seven Countries Study is summarised in Figure 2.

Figure 2: The food intake of Cretan men in the 1960s participating in The Seven Countries Study (Adapted from Kromhout et al., 1989)

1	at least 6 slices of stone-ground wholemeal sourdough bread
2	2–4 fresh fruits per day
3	2–3 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, 3–4 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 100–200ml per day, herbal teas (sage, sideritis) and ground coffee daily
11	herbs (mainly oregano), limited spices (mainly cinnamon)

First Mediterranean diet pattern score (MDPS)

The Seven Countries 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 food items and cuisines specific to these cultures. Therefore it remained in question whether mortality advantage could be replicated with the Mediterranean food pattern in non-Greek cultures.

Therefore, in 1995 a simple score was developed for the first time to assess adherence to the Mediterranean food pattern (but which did not directly incorporate food preparation/cuisine). The score was based on 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 applied to data collected for the Food Habits in Later Life study (FHILL) (Trichopoulou et al., 1995).

The Mediterranean diet pattern score (MDPS) was characterised by the following 8 food components (based on daily intake in grams/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 >25g women >50g men; score 1 if <25g women <50g men)

The design of the score favours a more plant based (or vegetarian) diet for which there is considerable evidence showing reduced mortality and morbidity from chronic diseases (in contrast to a more animal-based diet) (Leitzmann, 2005). 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. In contrast, a diet with fewer of these components (<4) would be less representative of this diet and therefore less healthy. These considerations are based on both epidemiological and biological evidence (Nestle 1999; Singh et al., 2003) (see Figure 3).

Figure 3: The National dish of Greece "Fasolada" (a soup made with haricot beans and vegetables) highlights the plant orientation of the traditional Greek

Values of 0 or 1 were assigned to each component by using the sex and cohort specific median intakes in g/day in the studied population as cut-offs. Food quantities in grams per day were adjusted using daily intakes of 2500 kcal for men and 2000 kcal for women. A value of 1 was assigned to components with a presumably beneficial effect (i.e vegetables, legumes, fruit and nuts, cereals, monounsaturated:

saturated fat ratio) and where consumption was above the median. A value of 0 was assigned to components with a presumably less beneficial effect (i.e meat, fish, dairy) and where consumption was equal to or above the median. For ethanol, a value of 1 was assigned to men who consumed quantities from 10g (or one unit) a day to less than 50g (or five units) a day and a value of 0 otherwise; the corresponding cut-offs for women were 5g a day and 25g a day. The MDPS values range from 0 (minimal conformity to the traditional Mediterranean diet) to 8 (maximal conformity to the traditional Mediterranean diet).

Elderly Greek 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 lifestyle 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 (first generation Greeks n=189 and Anglo-Celts n=141). Between 1989 and 1991 cross-sectional data were collected using validated questionnaires, along with blood tests and anthropometry. Mortality data were collected after 5 to 7 years (Wahlqvist et al., 2005).

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 second highest overall mortality followed by the Japanese and Swedes (see Figure 4).

Figure 4: Mortality risk ratio after 5 years follow-up for elderly cohorts in Greece (n=182), Melbourne (Greek-born n=189, Anglo-Celts n=141), Sweden (n=217) and Japan (n=89) (95% CI, Cox Proportional Hazards Regression) in the FHILL study (Source: Kouris-Blazos et al., 2002)


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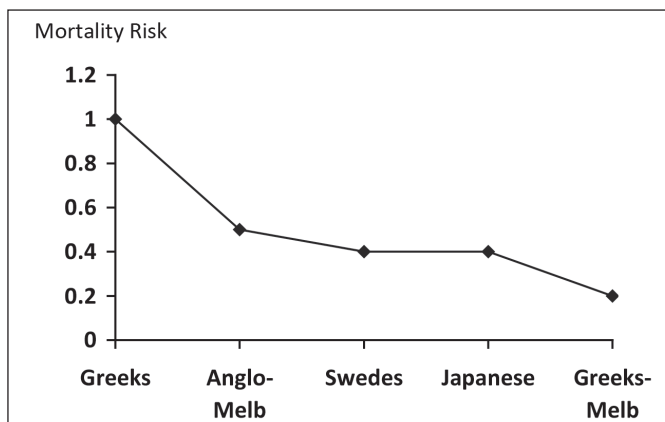
First study showing benefits of the Mediterranean diet pattern and legumes on longevity in old age

In order to understand the effect of diet and lifestyle on mortality, Kouris-Blazos et al., (1999) analysed the effect of the MDPS on survival in Greeks in Greece and Greeks in Australia. It was found that both elderly Greeks in Greece (n=182) (Trichopoulou et al., 1995) (see Figure 5) and Australia (n=189) (Kouris-Blazos et al., 1999) who adhered to the more plant-based Mediterranean dietary pattern (i.e had scores greater than or equal to 4) had a 50% reduced risk of death after 5 years.

Figure 5: 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 of 4 or more) (Kaplan Meier survival curves) (Source: Trichopoulou et al., 1995)
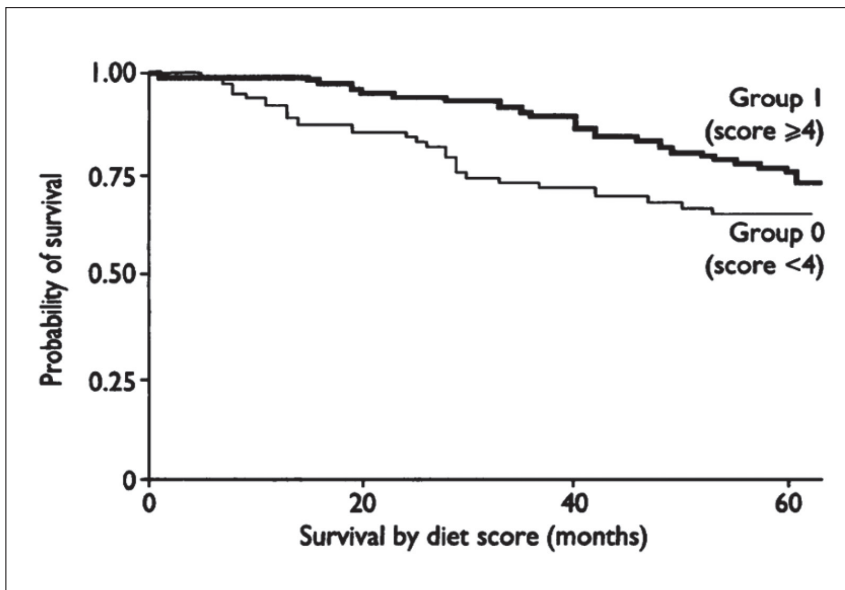
Interestingly, only 57% of Greeks in Greece were adhering to a Mediterranean diet compared to 81% of the elderly Greeks in Australia, which partly explained the 30% lower mortality in the latter. Furthermore, when the MDPS was applied to elderly Anglo-Celtic Australians (n=141) there was also a 50% reduced risk of death (only 28% were found to have scores greater than or equal to 4 which partly explained their 83% higher mortality than the Greek Australians). It was calculated that 37% of this mortality was due to lack of adherence to a Mediterranean dietary pattern (Kouris-Blazos et al., 1999).

Darmadi et al. (2004) investigated the relative importance of the individual components of the MDPS using data from FHILL (n=785). 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 20g consumed (*P*=0.02). A higher intake of fish and monounsaturated fat just failed to reach significance in the mortality relationship.

Trichopoulou et al. (2009) 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). 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 greater than 4 had a statistically significant reduction in total mortality by 28%. The contributions of the individual components to this association were moderate ethanol consumption 23.5%, low consumption of meat 16.6%, 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 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 lifestyle variables?

To determine how important the Mediterranean dietary pattern was relative to other psychosocial and lifestyle 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 scores 8) wellbeing 9) smoking 10) gender. This analysis revealed that the Mediterranean diet pattern was **more** important than most of the psychosocial and lifestyle 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). (Wahlqvist et al., 2005)

Has the Mediterranean diet pattern score (MDPS) been used in other 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. (2013) 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. This pioneering study assessed for the first time adherence to the Mediterranean diet by using a score".

A higher MDPS (or greater adherence to a Mediterranean dietary pattern) has consistently been shown to reduce overall mortality and mortality from cardiovascular disease. 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) (Trichopoulou et al., 2003). In Denmark (n=202) a one unit increase in the MDPS predicted a 21% (95% confidence interval 2-36%) reduction in mortality (Osler & Schroll, 1997). Interestingly, Danish subjects with high diet scores (> or = 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 (Trichopoulou et al., 2005).

A recent meta-analysis (Sofi et al., 2008) 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 cardiovascular disease and cancer, and the incidence of Alzheimer's and Parkinson's disease. 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 (Lasheras et al., 2000; Trichopoulou et al., 2003, 2005;) compared to studies done in Western European countries and Sweden (Lagiou, 2006), although no statistically significant heterogeneity existed (Sofi et al., 2008; 2010).

In two large Spanish cohorts (EPIC study) a higher score was linked to a 40% to 59% reduction in cardiovascular events (Martinez-Gonzalez et al., 2011; Buckland et al., 2009). 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 cardiovascular mortality and a 26% reduction in the onset of coronary heart disease (Trichopoulou et al., 2003). 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) (Knoops et al., 2004) as well as two large studies in the US (Mitrou et al., 2007; Fung et al., 2009). 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 cardiovascular mortality (Trichopoulou et al., 2005; 2007).

A higher score has also been associated with a lower risk of developing Alzheimer's disease (Scarmeas et al., 2006; Sofi et al., 2008; 2010), Parkinson's disease (Sofi et al., 2008; Gao et al., 2007) diabetes mellitus (Martinez-Gonzalez et al., 2008; InterAct Consortium 2011) and cancer (Lagiou 2006; Benetou et al., 2008; Sofi et al., 2008; 2010). 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) (Trichopoulou et al., 2003). 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 (Buckland et al., 2010).

The role of the Mediterranean diet in the development and management of obesity has always been of great interest for clinical research. Overall, studies have not found the Mediterranean diet high in olive oil to cause weight gain – quite the reverse (Shai et al., 2008). 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 body mass index and waist circumference (Romaguera et al., 2009). 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 (Panagiotakos et al., 2006). 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) (Schroder et al., 2004).

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 classical CVD risk factors like blood cholesterol, blood pressure or body weight. It is now thought that mechanisms involve oxidative stress, coagulation, endothelial function and inflammation (Delgado-Lista, J. et al., 2012), partly driven by a disturbed gut microbiome (Rogler and Rosano, 2013).

With respect to classical 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 (Kastorini et al., 2011). Olive oil and monounsaturated fat rich diets have been shown to lower blood pressure (Bondia-Pons et al., 2007; Gillingham et al., 2011). 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 hydroxytyrolsol, 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 B2, fibrinogen) (EFSA 2011; Delgado-Lista et al., 2011). 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 (Mordente et al., 2011). Resveretrol, a natural antioxidant found in red wine, has been shown to reduce oxidation of LDL cholesterol in in-vitro studies (Mukamal & Rimm, 2008).

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 (Delgado-Lista et al., 2011). 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 (Nadtochiv & Redman, 2011). Also, a study by Marin et al. (2011) showed that people following a Mediterranean diet improve the regenerative capacity of the vascular endothelium. 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) (Delgado-Lista et al., 2011).

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 (Jimenez-Gomez et al., 2010).

The Mediterranean diet has not only been shown to prevent the development of diabetes by more than 50% (Salas-Salvado et al., 2011) but also to improve the metabolic control of diabetes in a randomised clinical trial of Anglo-Celtic Australians (n=27) with diabetes, by decreasing glycated haemoglobin (Itsiopoulos et al., 2010). 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 (Hodge et al., 2010). 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 (Delgado-Lista et al., 2011).

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 (Wahlqvist, 2004). Instead of acute, ravaging infection which results in organ damage or death, it seems that the more common type of infections today are simmering, low grade ones that promote inflammation and oxidative stress, which in turn drive so called chronic disease and

may contribute to premature death. 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. The microbiome appears to play a crucial role in the development of a healthy gut and immune system, while disturbances have been associated with systemic inflammation and chronic diseases. Dysbiotic (pathogenic) bacteria release toxic substances, called lipopolysaccharides (LPS) and endotoxins, which cross the gut barrier and enter the host blood, leading to stimulation of inflammatory pathways via interaction with receptors on macrophages and causing "systemic inflammation". This is turn can affect the function of many organs, tissues and physiological systems contributing to metabolic syndrome, atherosclerosis and endothelial dysfunction (Table 2) (Rogler & Rosano, 2013; Bornigen et al., 2013; Taurog et al., 1994). A small intervention feeding study on 8 subjects (unpublished) by Dr Nanette Steinle of the University of Maryland's School of Medicine and Dr Emmanuel Mongodin of the University of Maryland Institute of Genome Sciences examined the effect of feeding a Mediterranean diet on the composition of the bowel microbiome. After 2 weeks there were no changes to the gut microbiome in the study subjects. Further studies are needed to examine the effect of the Mediterranean diet on the microbiome, immunity, and inflammatory markers.

How are the Greek Australians escaping premature death despite a high prevalence of classical CVD risk factors?

As discussed earlier, first generation Greek Australians who came to Australia from 1950 to 1970 continue to exhibit much lower mortality from heart disease and cancer despite a high prevalence of classical risk factors (established in the first 20 years in Australia due to the introduction of energy dense 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.

Brazionis et al. (2005; 2007; 2010) identified significantly higher blood carotenoid levels in Greek Australians aged 50–70 years (n=213) compared to Anglo-Celtic Australians (n=214) which was correlated with a lower prevalence of diabetic retinopathy. Furthermore, traditional foods consumed by migrant Greeks (such as leafy greens, figs, olive oil) have been found to be particularly high in carotenoids (Su et al., 2002). High blood carotenoids have been associated with lower overall mortality in elderly Danes following a Mediterranean dietary pattern (Osler and Schroll, 1997). Epidemiological studies suggest that diets high in carotenoid-rich fruits and vegetables are associated with reduced risk of cardiovascular disease 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 (Voutilainen et al., 2006).

Apart from having higher blood carotenoid levels, elderly Greek Australians may also have better endothelial function, less oxidative stress, thinner blood and less

systemic inflammation (hsCRP) protecting them from premature death, but more research is needed to confirm this. Further studies are also needed to examine the effect of the Mediterranean diet on the microbiome, immunity and inflammatory markers.

We propose that some of the health benefits observed with the Mediterranean diet are operating, in part, through the gut microbiome. Keeping the gut microbiome stable against the dominance of pathogens or dysbiotic bacteria is emerging as a possible factor in preventing and attenuating the progession of chronic diseases (see Table 2) (Cho and Blaser, 2012; Tilg and Kaser, 2011; Le Chatelier et al., 2013; Wang et al., 2011; Qin, 2012).

Table 2: Disease states and conditions that have been associated with altered gastrointestinal microbiota (adapted from Sanders, 2011; Binns, 2013; Cho & Blaser, 2012)

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

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. The good bacteria in the large bowel (*Lactobacillus, Biffidobacterium, Eubacterium*) ferment prebiotics to produce beneficial metabolites (such as short chain fatty acids) which are absorbed into the blood stream and exert a beneficial health effect by modulating the immune and inflammatory responses of the host (Binns, 2013). The metabolites also remain in the gut to promote and maintain bowel health and function and absorption of minerals. It has been known for a long time that prebiotics include carbohydrates and dietary fibre such as polysaccharides (e.g pectins, hemicelluloses, gums, inulin, resistant starches), oligosaccharides (raffinose, stachyose, galacto-oligosaccharides, fructo-oligosaccharides), sugars (lactulose, non-absorbed lactose and fructose) and polyols (mannitol, xylitol, maltitol, isomalt). However, recently it has also been demonstrated for other food constituents, particularly phytochemicals like polyphenols (Tomas-Barberan & Mine, 2013). Also, consuming fermented foods

(probiotics) high in beneficial *Lactobacilli* and *Biffidobacteria* can also contribute to a healthy microbiome. In contrast, protein fermentation in the bowel is considered more detrimental for human health as it results in the production of potentially toxic carcinogenic substances such as ammonia, amines, phenols and sulphides (Binns, 2013).

The plant-based Mediterranean diet is high in both probiotics and prebiotics with the potential to favourably influence the gut microbiome which in turn may reduce circulating endotoxins and lipopolysaccharides and the development or progression of CVD risk factors (Bested et al., 2013) (Table 3). Furthermore the diet contains foods/herbs/spices with anti-microbial properties which may improve the gut microbiome by reducing dysbiotic bacteria (Table 3). Also, adherence to the Mediterranean diet by traditional communities is usually coupled with religious fasts. This involves vegan eating for at least 40–100 days of the year. Restriction of animal protein, saturated fat, calories and weight loss, may also have a beneficial effect on the gut microbiome (Cotillard et al., 2013). 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 (Vlassara and Striker, 2013) and potentially the microbiome.

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

Probiotics	fetta cheese, yoghurt, olives, trahana (fermented wheat and milk)
Prebiotics	legumes, nuts, grains, vegetables (especially onions, garlic, wild greens, artichokes), fruits (especially grapes, citrus, pomegranate), olives, olive oil, coffee, herbs, spices, honey
Antimicrobials	olives, olive oil, clove, cinnamon, oregano, thyme, sage, sideritis, chamomile, mint, lemon, wine, spirits
Cuisine	more casseroles, soups and raw food and fewer roasts, grills and barbeques
Higher proportion of plant foods relative to animal foods Fasting from animal foods and animal fats (for religious reasons)	

Understanding the links between the microbiome, diet and human disease may provide prophylactic or therapeutic tools to improve human health. We have the opportunity to examine some of these questions with the Mediterranean Island Study (Thodis et al., 2014; Tsindos et al., 2014) and the Cardiac Intervention study conducted by the Department of Dietetics and Human Nutrition at La Trobe University to better understand how CVD risk factors can be made "benign" or prevent them from happening in the first place.

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