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Prospective evaluation of cardiovascular-risk surrogates via lifestyle and adherence to the Mediterranean diet: Results from PERSEAS/The Elafonisos-Area Study

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Abstract

Background: Lifestyle and nutrition are main causes of obesity, and cardiovascular disease. PERSEAS (Prospective Evaluation of vascular-Risk Surrogates: the Elafonisos-Area Study) is an epidemiological prospective study aiming to assess the physical course of cardiovascular risk-factors, including adverse lifestyle habits, and their complications in the closed rural area of Elafonisos-Island, Greece.

Methods: PERSEAS is a 5-year primary population study, with a 1-year visit elapsing period, which recruited 612 local individuals. Trained medical/paramedical personnel performed annual visits from 2012 to 2016. All participants were interviewed, and clinically evaluated.

Results: PERSEAS concluded that the Mediterranean-diet model is not faithfully adopted in the Greek rural populations. This was accompanied by physical inactivity, increased rates of obesity, hypertension, hyperlipidemia, and type 2 diabetes (35%-50%). Coronary heart disease (CHD, 6.1%), and peripheral artery disease (PAD, 6.3%) were the most prevalent cardiovascular complications compared with stroke (1.8%), or atrial fibrillation (2%). Older people (≥ 65years) suffered more from PAD [Odds-Ratio, 95%C.I.:2.49 (1.03-5.98)]. Type 2 diabetes was associated with higher stroke incidence [2.61 (1.03-6.74)]. Women suffered more from stroke, CHD, or atrial-fibrillation, by almost 7-fold. Obesity was the only major risk-factor associated with all four morbidity conditions (CHD, PAD, stroke, and atrial-fibrillation).

Conclusion: Aggressive lifestyle changes and early treatment of risk-factors should be pursued to reduce the burden of cardiovascular disease in rural populations in Greece. Appropriate public health measures for improving dietary patterns, and the global trend of "Western" nutritional transition at population level should be established.

Introduction

Several epidemiological studies have demonstrated that metabolic risk-factors, such as hypertension, diabetes, and hyperlipidemia are associated with increased prevalence of cardiovascular complications [1,2]. Prospective studies further suggest that they are also associated with increased incidence of future cardiovascular events [3,4]. Unhealthy lifestyle, described by physical-inactivity, increased alcohol consumption, imbalanced diet, and poor sleep, increases cardiometabolic-risk, and is closely associated with a higher prevalence, and incidence of cardiovascular disease (CVD) [5,6]. Randomized controlled trials have demonstrated that medication together with healthy lifestyle measures, such as regular exercise, and diet to achieve body-weight reduction, can reduce the burden of cardiovascular morbidity [7,8].

Between countries, and even among regions, there is great variability in the prevalence of cardiovascular risk-factors, and the rate of complications [9,10]. This has been attributed to different lifestyle, and genetic background [11]. For example, stroke incidence in Asian populations is by far higher compared with Europeans [12]; CVD incidence is higher in Northern-Europe compared with the Mediterranean-Sea [13]; and finally, higher longevity is observed in well-confined areas of one country, as was demonstrated in Ikaria-Island, Greece [14].

An important problem with epidemiological studies is that the observed population may be composed of subjects with different socio-demographic, and genetic characteristics because of increased rate of inward migration. Therefore, when an epidemiological study is

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prospectively planned, the observed population should be constant, and without substantial permanent outward migration. In all prospective epidemiological studies, the "Hawthorne-effect" cannot be neglected, thus the alteration of behavior by the studied subjects due to their awareness of being observed by investigators, even in the absence of interventions [15]. This phenomenon can be further increased by alternative factors, such as publicity, and diagnostic-measures, that may interfere, and change behaviors of the participants. Finally, different educational activities during the study promoting healthy lifestyle may be allowed.

In Greece, different epidemiological studies have been conducted to study the prevalence of cardiovascular risk-factors. Some of these studies were performed in open populations, like the ATTICA-study [16] in Athens. By contrast, other studies were performed in closed populations like the DIDIMA-study (Northern-Peloponnesus) [17], and the IKARIA-study [14], aiming to assess the prevalence of hypertension, and the secrets of longevity, respectively. However, all of these studies were not designed prospectively, and any reported long-term results were based on *post-hoc* decisions.

PERSEAS (Prospective Evaluation of vascular-Risk Surrogates: the Elafonisos-Area Study) is an epidemiological prospective study aiming to assess the physical course of cardiovascular risk-factors, including adverse lifestyle-habits, and their complications in a closed rural-area of Greece. We performed a 5-year follow-up with a 1-year visit elapsing period to promote possible beneficial changes in lifestyle-habits, and an associated change on risk-factor profile. We hoped that conclusions derived from this study, may be used for providing more targeted preventive actions against CVD in Greece.

Materials and Methods

Study design

The entire study protocol took place in the local Health Unit of Elafonisos-Island, Greece. The study was conducted under the auspices of the Greek Ministry of Health, the Municipality of Elafonisos, and the Medical Association of Lakonia, according to the guidelines by the Declaration of Helsinki. All procedures involving humans were approved by the National-Organization for Medicines which acted as an ethics/committee. The study-staff was made by trained medical/paramedical personnel, all members of EMPAKAN, a Greek Medical-Society for the Study of Vascular Risk-Factors. The local medicinal authority collaborated with the study investigators to provide information about the medical history of the participants. Each visit was made annually during two pre-specified weeks of each September from 2012 to 2016. The study started in 2012 (first stage) and ended in 2016 (fifth and final stage).

Cohort description

The target population consisted of all permanent inhabitants of Elafonisos-Island, aged 15years/or older, during the study-period. All participants were interviewed and underwent full clinical evaluation. The reference population (total number of the island adult inhabitants) was defined according to the 2011 census of the Greek population by the National Statistics-Agency [http://www.statistics.gr/en/2011-census-pop-hous, last-accessed on 09/01/2016].

Patient and public involvement

Patients and the general public did not have direct involvement in the design of this study, recruitment, or the development of research questions, or measures. Written informed consent was obtained from all subjects. Collection and data analysis was done anonymously, but all participants had access to the results of their analyses provided to them by the local medical authority. On publication, patients will be sent a copy of the article, which would not have been possible without their participation.

Materials and measurements

Dietary-score and healthy habits index

A dietary-score was created, based on eleven questionnaire-elements: whole-grain cereal, fruits/juice, vegetables/salads, legumes, fish, red-meat, poultry, full-fat dairy, olive-oil, normal-fat cheese, and alcohol consumption. Each of these ingredients' consumption levels were collapsed to two levels (0, 1), with sex-specific median values used as cut-off points. The sum of these values per person, corresponded to his/her dietary score. The rationale of the mapping was the following: for food categories considered to be beneficial to health value 1 was attributed for people consuming quantities above the sex-specific median. The inverse logic was applied to ingredients that are known to be non-beneficiary to health: people consuming quantities equal/or more than the sex-specific median scored 0. Therefore, the dietary-score was merged into 3 categories: "Bad" (0-3)," Normal" (4-7), and" Good" (7-11) nutritional habits. Based on daily alcohol consumption value 1 was attributed to men consuming ≥3glasses/day, and for women consuming ≥ 2glasses/day. People consuming no alcohol at all were attributed the value 0, irrespective of gender. Value 0 was credited to current-smokers, 1 to former-smokers, 2 to never-smokers. Regarding physical activity, we assigned 0 to <3times/week, and 1 to at least 3times/week. Dietary-score, alcohol consumption, smoking, and physical activity were all incorporated into the construction of a general daily health-habits index, which ranged from 0 to 10 (unhealthy towards healthy).

Other questionnaire-based variables

All participants were asked about their educational status. The usually consumed alcoholic-beverage was registered for each participant. All participants were asked to provide the approximate number of sleeping-hours/per day. Established CVD (stroke/or coronary-heart-disease, CHD), and cardiovascular risk-factors (diabetes, hyperlipidemia, and hypertension) were diagnosed on the basis of patient reporting, or/and referred medical history, or/and relative medication regimen. Unknown diabetes (screen-detected) was diagnosed according to WHO-criteria, based on either a fasting-glucose ≥ 7.0mmol/L, or an HbA1c ≥ 6.5%. The cut-off values for diagnosing prediabetes were also based on WHO-criteria i.e., fasting-glucose 6.1-6.9mmol/L, or/and HbA1c 6.0-6.4%. Unknown hypertension was diagnosed when at least two BP measurements were ≥ 140mmHg/90mmHg. Additionally, unknown hyperlipidemia was considered when serum total-cholesterol was ≥ 6.2mmol/L. Peripheral artery disease (PAD) was diagnosed based either on history/or on impaired ankle-brachial-pressure-index (ABI) measures (<0.90). Similarly, atrial-fibrillation (permanent/paroxysmal) diagnosis was based either on history/or on ECG-pattern performed during the visit.

Measurements

All participants underwent height/and weight measurements on site. An average of two measurements of height was obtained with a calibrated anthropometer. Body weight was determined using a digital-scale. BMI was calculated. Waist-circumference, measured at the

midpoint between the costal-margin, and iliac-crest were also assessed. BP was measured according to the European-Society of Hypertension/Cardiology guidelines (2013) by use of a validated electronic-device (M2 Basic Upper-Arm BP/Monitor, Omron). Hypertension was defined as systolic BP ≥ 140mmHg, and/or diastolic BP ≥ 90mmHg. Diagnosis of hypertension was based on two BP measurements in the sitting position. Patients with elevated BP were re-evaluated on a second visit. Capillary blood-samples were obtained to measure glucose, HbA1c, and lipid-profile by using separate validated kits. A validated point-of-care portable analyzer was used to measure plasma lipids, and glucose-levels (CholestechLDX®Laboratory Procedure, Alere) in a 40μL blood-sample, taken from a fingerstick. A second desktop point-of-care analyzer was used for measuring HbA1c, in a blood-sample of 4μL, drawn from the same fingerstick (Quo-Lab™ A1C, EKF Diagnostics). ABI was measured as the ratio of the systolic BP at the ankle to the BP in the same side upper arm. Left and right ABI estimates were registered. Measurements were obtained by using a Doppler-device, and appropriate cuff placed over the posterior-tibial, and brachial-artery. An ECG was performed in all subjects during each visit.

Statistical analysis

Apart from descriptive statistics for the 5-years of the study, inferential analysis was also performed. Due to the longitudinal nature of the study, the methods of analysis used were those of Generalized Linear Mixed-Effects Models (GLMM), Cumulative Link Mixed Models (CLMM), and Generalized Estimation Equation Models (GEE). The whole analysis was conducted using R (v.3.4.2), and R-libraries lme4 (v.1.1-10), ordinal (v.2015.6-28) and gee (v.4.13-19). GLMM and CLMM models were used appropriately, depending on the nature of the variables with participants as the grouping factor. Statistical significance level was set to 5%, for all comparisons.

Results

Study identity and variable changes

The initial study population included 612 individuals (76.5% of the island's target population), who agreed to participate, and signed an informed consent. Almost 400 individuals (65%) provided fully completed questionnaires and underwent full clinical/laboratory assessment during the first visit. During the final (fifth) stage of the study, 352 people participated, of whom 303 were present in at least one previous stage, while 49 were first-time participants. Overall, 120 persons (17.2%) participated in all 5 stages of the study, 88 (12.6%) in four, 109 (15.6%) in three, 139 (19.9%) in two, while 243 (34.8%) have taken part only in one stage. The age of the participants during the fifth stage was 52.7 ± 19.6years (mean value ± SD), while 35.5% of participants were ≥ 65years. The majority of the participants (57.9%) had no education, while 42.1% had graduated from secondary school. BMI increased across the visits (p=0.03) and measured 27.8Kg/m^2 in the last visit. Fruits/vegetables were consumed in a daily-basis from 40-45% of participants; fish-consumption was reported frequently (70-75%); while olive-oil was constantly present on the table of almost all inhabitants (98.8%). Although, there was a progressive increase in alcohol consumption (p<0.001), the overall prevalence of drinkers compared with no drinkers was not different (20%). Among alcohol beverages, wine was used more frequently (56.4%). During the entire study-period almost 35% of participants were current-smokers, and 48% were never-smokers. Daily physical activity was performed by 8% of the participants, whereas 15% exercised 3times/weekly. The healthy-habits index was optimal/or sub-optimal (6/or 5-points respectively) in almost 1/3 of the participants. Overall, there was a significant increase in the percentage of hyperlipidemia at study-end (29.6% *vs.* 43.8%, p=0.006). Type 2 diabetes increased from the first to the following visits and remained constant throughout the three last years of the follow-up (6.3% *vs.* 12.5%, p=0.03). PAD significantly increased in all study periods (91% *vs.* 96.1%, p=0.001). By study end, 52.1% of the participants were hypertensives, and 35% were obese. Of note that in the last visit, 29% of the participants had prediabetes. The overall rate of CHD, stroke, PAD, and atrial fibrillation were 6.1%, 1.8%, 6.3% and 2%, respectively.

Table 1: Association of population's characteristics with age group (Reference category: Age <65 years)

Variable	Odds Ratio	95% C.I.	*p*-value
Age (Years)	4.700	(3.67-5.72)	<0.001
Sleep per day (hours)	0.570	(0.80-0.34)	<0.001
Dietary score	1.490	(1.25-1.72)	<0.001
Height (cm)	0.280	(0.14-0.41)	<0.001
Weight (kg)	2.730	(1.00-4.47)	<0.001
Waist circumference (cm)	5.020	(3.05-6.98)	<0.001
Body fat (%)	1.670	(1.65-2.68)	<0.001
Lean body-mass (kg)	3.180	(1.17-5.20)	<0.001
LDL (mg/dl)	0.720	(0.36-0.98)	<0.001
Non-HDL Cholesterol (mg/dl)	0.640	(0.27- 0.90)	0.01
Fasting Glucose (mg/dl)	11.210	(8.23-14.17)	<0.001
HbA1c (%)	1.310	(1.21-1.41)	<0.001
ABI (Left)	0.010	(0.0-3.0)	0.04

Table 2: Association of population's characteristics with gender (Reference category: Males)

Variable	Odds Ratio	95% C.I.	*p*-value
Age (Years)	6.87	(5.01-8.73)	<0.001
Dietary score	0.31	(0.08-0.53)	0.01
Weight (kg)	6.42	(4.10-8.71)	<0.001
Body-mass index (BMI) (kg/m^2)	1.53	(1.31-2.11)	<0.001
Waist circumference (cm)	0.83	(0.59-0.06)	<0.001
Total cholesterol (mg/dl)	8.14	(3.18-13.09)	<0.001
HDL cholesterol (mg/dl)	8.56	(6.61-10.52)	<0.001
Glucose (mg/dl)	0.40	(0.34-0.46)	<0.001
HbA1c (%)	0.11	(0.00-0.21)	0.04
Ankle-Brachial Pressure Index	0.02	(0.01-0.04)	<0.001

Analysis by age

As shown in Table 1, older participants had statistically significantly higher dietary-score, compared to younger persons. Waist-circumference, and body-fat percentage was higher in older participants, while height was lower. Older persons were found to get less hours of sleep per day. Elevated glucose, and HbA1c levels were both associated with age of 65 years/or more. Finally, age over 65 years was associated with lower LDL-levels, and ABI, compared to younger participants, at the time of participation.

Analysis by gender

In Table 2, statistically significant results for between gender comparisons are presented. Women demonstrated lower waist-circumference, but higher BMI, compared to men. Total-cholesterol, and HDL-cholesterol levels were higher in women. Dietary score was slightly lower in women compared to men. Additionally, glucose, HbA1c levels, and ABI, were all reported/measured lower in female participants.

Table 3: Association of the subjects' last participation in the study with measured characteristics, for participants with two/or more visits (Reference category: First visit)

Variable	Odds Ratio	95% CI	*p*-value
Weight (kg)	1.275	(1.026-1.651)	0.041
BMI	3.497	(2.264-3.551)	<0.001
Total -cholesterol (mg/dl)	1.631	(0.614-0.648)	0.004
LDL-cholesterol (mg/dl)	1.709	(0.251-0.788)	<0.001
HDL-cholesterol (mg/dl)	0.172	(1.431-3.913)	0.015
HbA1c (%)	1.095	(1.029-1.162)	0.005
ABI	0.033	(0.016-0.046)	<0.001
Hypertension (yes)	1.323	(1.161-1.845)	0.003
Alcohol	1.984	(1.35-2.952)	0.001
Whole-grain products	0.679	(0.496-0.921)	0.013
Fruits-Juice	0.768	(1.56-10.109)	0.005
Poultry/Fish	1.173	(1.028-1.755)	0.031
Dairy products	0.716	(0.525-0.967)	0.03
Cheese	8.579	(2.907-3.551)	<0.001
Sweets	1.092	(1.033-1.223)	<0.001
Physical activity	0.678	(0.492-0.928)	0.016

Comparison between first and last visit

Comparison of the measured variables' evolution between the two more distant visits, for all participants having participated at least twice, revealed that weight, and BMI had increased (Table 3). Total, and LDL-cholesterol had also increased since the participants' first visit, while HDL-cholesterol had decreased. HbA1c was found higher during the last visit, while ABI had decreased. Participants were more likely to report consuming alcohol at their last participation. Consumption of whole-grain products, fruits/juice, vegetables/salads, had decreased, whereas consumption of red-meat, and cheese had increased during the last participation. Poultry/Fish, and sweets was consumed more frequently prior to the last participation. Physical inactivity was more frequent, and hypertension was more observed at the last visit.

Association between risk-factors and CVD

Table 4 presents the association of major risk-factors with four CVD conditions recorded during the 5-years of the study: CHD, stroke, PAD and atrial-fibrillation. Older people (≥ 65years) suffered more from PAD, compared to their younger counterparts, after adjustment for gender, hypertension, type 2 diabetes, smoking, and hyperlipidemia. As expected, type 2 diabetes was associated with higher incidence of stroke. There was an association of gender with all CVD, except for PAD, with females being more prone to have suffered stroke events, CHD or atrial-fibrillation, after adjustment for all the other risk-factors included in the model. Of importance, obesity was the only major risk-factor associated with all four CVD conditions during the 5-years study.

Discussion

Main findings

PERSEAS suggests that even in a small Eastern-Mediterranean Island like Elafonisos, the healthy diet-model based on fruits, and vegetables is not faithfully adopted. However, some of the key Mediterranean-diet elements, such as olive-oil, and fish consumption are not abandoned. Alcohol consumption was more than moderate in most of the participants, while daily physical-activity was limited. These lifestyle habits remained unchanged throughout the 5-year follow-up period, suggesting that Greek rural populations have adapted many aspects of the "Western" lifestyle, like physical inactivity, increased red-meat, and high glycemic-index products consumption. This adverse lifestyle was also accompanied by increased rates of the overweight/and obese phenotype. Moreover, the rates of hypertension, hyperlipidemia, and impaired glucose patterns (prediabetes/or type 2 diabetes) were steadily high, ranging from 35% to 50% during the different follow-up period visits. Participants had impaired lipid-profile, and ABI measurements from the first, and the following visits, however, this knowledge was not accompanied by prospectively trying to adapt a healthier lifestyle attitude. Cardiovascular complications demonstrated a stable representation throughout the follow-up period with CHD, and PAD being the most prevalent compared with stroke, or atrial fibrillation.

Older participants (≥ 65years) demonstrated a healthier dietary profile, and this attitude was accompanied by lower hyperlipidemia rates. However, the prevalence of type 2 diabetes was not positively affected. This may be partly attributed to the increased waist-circumference, and BMI rates observed in the elderly, thus suggesting that obesity was more prevalent. As expected, ABI was more reduced in older participants, probably due to aging. Dietary score in women was more adverse compared with men. Prevalence of hyperlipidemia, diabetes/prediabetes, and PAD were also more increased in women. Female gender was an important determinant of stroke, CHD and atrial fibrillation. Obesity was the only major metabolic risk-factor significantly, and independently associated with increased CVD risk throughout the 5-years of study.

Comparison with previous studies

The prevalence of hypertension was more increased in PERSEAS compared with the ATTICA-study16 performed in the early 2000 in the greater urban area of Athens, Greece (50% *vs.* 32% respectively). The same was relevant for the prevalence of hyperlipidemia (44% in PERSEAS *vs.* 35% in the ATTICA). Obesity was 17% in the ATTICA cohort *vs.* 35% in the population of PERSEAS, while diabetes was 8% vs. 12.5% respectively. CHD rates were similar in the two cohorts (6%). The adherence rate to the Mediterranean-diet was almost 30% in both the ATTICA and

Table 4: Association of risk factors with cardiovascular disease. Data are presented as Odds Ratio (95% Confidence Interval) after adjustment for gender, age, smoking (yes), obesity (yes), hypertension (yes), Type 2 diabetes (yes), and hyperlipidemia (yes)

	Stroke	Coronary heart disease	Peripheral artery disease	Atrial fibrillation
Gender (Female)	7.32 (2.27-23.63)***	3.63 (1.44-9.13)**	1.35 (0.75-2.42)	7.03 (2.35-21.05)***
Age (≥ 65 years)	1.20 (0.46-3.15)	0.64 (0.31-1.29)	2.38 (1.29-4.40)**	1.07 (0.4-2.73)
Smoking (Yes)	1.26 (0.70-2.26)	1.39 (0.65-2.82)	0.59 (0.33-1.06)	1.43 (0.57-3.62)
Obesity (Yes)	1.20 (1.00-17.95)*	2.49 (1.03-5.98)***	3.11 (1.20-8.04)**	2.35 (1.00-5.85)**
Hypertension (Yes)	1.86 (0.72-4.85)	1.04 (0.59-1.82)	0.81 (0.46-1.42)	1.29 (0.62-2.69)
Type 2 diabetes (Yes)	2.61 (1.01-6.74)*	1.50 (0.79-2.84)	1.12 (0.44-2.84)	0.89 (0.31-2.58)
Hyperlipidemia (Yes)	1.51 (0.79-2.88)	0.80 (0.54-1.19)	1.50 (0.91-2.48)	0.68 (0.34-1.35)
Observations (n)	1,561	1,562	1,562	1,559

***Significant at the 0.1 percent level; **Significant at the 1 percent level; *Significant at the 5 percent level

the PERSEAS studies. Although, the two populations are hardly comparable, they share similarities in the prevalence of risk-factors, and the rates of unhealthy lifestyle, thus resulting in an equal frequency of CHD. It should be acknowledged that ATTICA was conducted in a time-period during which the income in Greece was more increased, compared with the latter years in which economic-crisis is pronounced in both urban/and rural areas. In accordance with our results, recent studies indicate that during the European economic-crisis, fruit/and vegetable consumption alarmingly decreased, especially among those of lower socio-economic status, whereas trends in smoking prevalence, and physical activity were favorable [18,19]. These results suggest that economic-crisis has an unequal impact on different cardiovascular risk-factors among various socio-economic groups, although its overall health influence might be neutral.

The Ikaria-study [14] was a small-scale survey of the diet, and lifestyle of elderly Greeks (>80years) on Ikaria-Island. The main findings revealed a lower prevalence of cardiovascular risk-factors in the elderly cohort, attributed to a higher adherence to the Mediterranean-diet, habitual physical activity, noon-siesta, and engagement in social activities. The prospective results of the Ikaria-study are lacking in PERSEAS. Although, the elderly cohort of PERSEAS was more attached to a healthier lifestyle compared with the younger people, there was a high prevalence of cardiovascular risk-factors in both age-related strata (>65years *vs*. <65years). Taken together the elderly people in both Ikaria and Elafonisos-Island demonstrated an overall healthy lifestyle, but this attitude in Elafonisos, at variance with Ikaria, was not associated with decreased rates of CVD morbidity.

Conclusions

The present study demonstrated a marginal adherence to the Mediterranean-diet, and a high risk-factor prevalence in the rural population of Greece. Among cardiovascular risk-factors the prevalence of hypertension was almost 50%, type 2 diabetes 13%, hyperlipidemia 45%, and obesity 35%. High rates of overweight phenotype, and prediabetic state were also observed (30%). These adverse lifestyle, and risk-factor profiles increased throughout the 5-year follow-up period. In the rural area of Elafonisos, cardiovascular complications were not different compared with those of an urban area of Greece, and were strongly related to female gender, and obesity status. Our findings confirm that aggressive lifestyle changes, and early treatment of risk-factors should be pursued to reduce the burden of CVD in Greece. Strategies against the obesity epidemic might be a crucial intervention to reduce heighten cardiovascular risk. Therefore, it is important to establish appropriate public health measures for improving dietary patterns, and the global trend of "Western" nutritional transition at the population level.

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Author Contributions

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