Relationship Between Healthy Diet and Risk of Cardiovascular Disease Among Patients on Drug Therapies for Secondary Prevention

A Prospective Cohort Study of 31 546 High-Risk Individuals From 40 Countries

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Background—Diet quality is strongly related to cardiovascular disease (CVD) incidence, but little is known about its impact on CVD events in older people at high risk of CVD and receiving effective drugs for secondary prevention. This study assessed the association between diet quality and CVD events in a large population of subjects from 40 countries with CVD or diabetes mellitus with end-organ damage receiving proven medications.

Methods and Results—Overall, 31 546 women and men 66.5±6.2 years of age enrolled in 2 randomized trials, the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET) and the Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects With Cardiovascular Disease (TRANSCEND), were studied. We used 2 dietary indexes: the modified Alternative Healthy Eating Index and the Diet Risk Score. The association between diet quality and the primary composite outcome of CV death, myocardial infarction, stroke, or congestive heart failure was assessed with Cox proportional hazard regression with adjustment for age, sex, trial enrollment allocation, region, and other known confounders. During the 56-month follow-up, there were 5190 events. Patients in the healthier quintiles of modified Alternative Healthy Eating Index scores had a significantly lower risk of CVD (hazard ratio, 0.78; 95% confidence interval, 0.71–0.87, top versus lowest quintile of modified Alternative Healthy Eating Index). The reductions in risk for CV death, myocardial infarction, and stroke were 35%, 14%, and 19%, respectively. The protective association was consistent regardless of whether patients were receiving proven drugs.

Conclusions—A higher-quality diet was associated with a lower risk of recurrent CVD events among people ≥55 years of age with CVD or diabetes mellitus. Highlighting the importance of healthy eating by health professionals would substantially reduce CVD recurrence and save lives globally.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00153101.

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Key Words: cardiovascular diseases ■ diet ■ epidemiology ■ nutritional status ■ secondary prevention

Each year, at least 20 million people worldwide survive a heart attack or stroke.[1] Individuals with cardiovascular disease (CVD), diabetes mellitus, or end-organ damage have increased risk for another event or new CVD events compared with healthy individuals. Antiplatelet agents, statins, angiotensin modulators, and β-blockers each reduce the risk of CVD events by about one quarter, and their combined effects are projected to be substantial.[2] Epidemiological studies have shown a lower risk of CVD events associated with healthy diets in those without prior CVD.[3] There are few

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Table 1. Baseline Characteristics of Participants According to Quintiles of the mAHEI

Variable	Q1 (n=6307)	Q2 (n=6312)	Q3 (n=6307)	Q4 (n=6309)	Q5 (n=6311)
Median score	16.0	20.5	24.3	28.7	35.7
Age, mean (SD), y	66.3 (7.3)	66.4 (7.2)	66.6 (7.2)	66.6 (7.2)	66.7 (7.3)
Education n (%)					
Up to high school, n (%)	4422 (70.1)	4258 (67.4)	4139 (65.6)	3793 (60.1)	3350 (53.1)
Trade school, college, university, n (%)	1865 (29.6)	2051 (32.5)	2167 (34.4)	2516 (39.8)	2960 (46.9)
Current smoker, n (%)	969 (15.4)	803 (12.7)	737 (11.7)	695 (11.0)	603 (9.6)
Alcohol use, n (%)	1143 (18.1)	1860 (29.5)	2426 (38.5)	3028 (48.0)	3742 (59.3)
Adhered to medication, n (%)*	4245 (67.4)	4199 (66.6)	4195 (66.6)	4138 (65.6)	4180 (66.2)
Physical, n (%)					
2–4 times/wk, n (%)	1358 (21.5)	1367 (21.7)	1409 (22.3)	1492 (23.6)	1569 (24.9)
5–6 times/wk, n (%)	421 (6.7)	464 (7.4)	418 (6.6)	490 (7.8)	607 (9.6)
BMI, mean (SD), kg/m^2	28.5 (4.7)	28.3 (4.7)	28.3 (4.6)	27.9 (4.5)	27.5 (4.3)
Gained weight, n (%)†	2270 (48.9)	2238 (46.9)	2224 (45.5)	2297 (45.9)	2430 (47.8)

mAHEI indicates modified Alternative Healthy Eating Index; Q, quintile; and BMI, body mass index.
*P for trends for adherence to medication (yes, %) was 0.08 for mAHEI.
†P for trends for weight gain was 0.2.

prospective studies of diet quality and CVD outcomes in people with established CVD,[4,5] and it is unknown whether dietary benefits are additive to the effects from drug treatments used in secondary prevention. Although randomized trials are the most reliable form of evidence for assessing causal relationships, this approach is less amenable to study long-term dietary effects on CVD outcomes because of the impossibility of patient blinding, substantial noncompliance over time, and crossover. Thus, observational cohort studies provide the most feasible approach to evaluating long-term dietary efficacy. Importantly, observational cohort data of CVD patients can help to address the relationship of dietary patterns in high-risk individuals who are already receiving proven drugs and to assess whether healthy eating patterns are associated with a lower risk of CVD events.

Clinical Perspective on p 2712

In this study, we prospectively assessed the association between diet quality and the risk of CVD events in the 31 546 high-risk participants enrolled in the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET) and the Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects With Cardiovascular Disease (TRANSCEND).

Methods

ONTARGET and TRANSCEND were 2 parallel, multinational, double-blind, randomized trials evaluating the effects of telmisartan, ramipril, or their combination (ONTARGET) or telmisartan versus placebo (TRANSCEND) in 733 centers in 40 middle- and high-income countries coordinated by the Population Health Research Institute, McMaster University and Hamilton Health Sciences (Hamilton, Canada); Oxford University (Oxford, UK); and University of Auckland (Auckland, New Zealand). Both studies were approved by the institutional review committees of the centers, and their designs and main findings have been reported previously.[6–9]

Study Population

Overall, 31 546 individuals (9378 women, 22 168 men; ONTARGET, 25 620 angiotensin-converting enzyme inhibitor tolerant; TRANSCEND, 5926 angiotensin-converting enzyme inhibitor intolerant) ≥55 years of age with a history of coronary, peripheral, or cerebrovascular disease or diabetes mellitus with end-organ damage gave informed consent and were randomly assigned to ramipril, telmisartan, or their combination in ONTARGET and to either telmisartan or placebo in TRANSCEND, following similar protocols, procedures, study forms, and visits. Both ONTARGET and TRANSCEND did not include patients with acute coronary syndrome, acute stroke, congestive heart failure (CHF), and important renal insufficiency. Median follow-up was 56 months for both studies and varied from 53 months (Mexico) to 60 months (Taiwan). Participants were evaluated at 6 weeks and 6 months after randomization and every 6 months thereafter; 99.8% of participants in ONTARGET and 99.7% in TRANSCEND were followed up until the first primary outcome or the end of the study. The discontinuation of ONTARGET study medication was 24.5% for ramipril, 23.0% for telmisartan, and 29.3% for combination therapy.[7] Fewer patients receiving study medication discontinued the medication (36.9%) than those receiving placebo (38.5%) in TRANSCEND.[9] However, all events in those who discontinued the study medications were recorded.

Outcome

The primary outcome in both trials was the first occurrence of the composite of CVD death, nonfatal myocardial infarction (MI), nonfatal stroke, or hospitalization for CHF. Each component of this composite, all deaths, and all cancers were adjudicated on the basis of prespecified definitions by a committee blinded to the randomized medications and unaware of the dietary assessment results.

Data Collection and Measurements

Information was obtained by standardized questionnaire at baseline on age, education, ethnicity, and lifestyle, including diet, physical activity, smoking (never, current, former), daily alcohol intake (frequency of intake), fasting lipids, and glucose.[6] Medications, physical activity, blood pressure, body mass index (BMI), waist circumference, and hip circumference were also recorded at baseline, at 2 years, and at the study end.

Dietary Assessment

We recorded patients' food intake using a qualitative food frequency questionnaire (FFQ) that contained 20 food items, originally used in the INTERHEART study (conducted in 52 countries) and provided in Table I in the online-only Data Supplement. The FFQ interview, administered at the time patients were randomized, took ≈10 to 15

minutes to complete. Participants were asked, "In the last 12 months, how often did you eat foods from each of the following categories?" A list of food items was given. Because this FFQ was designed for use in international studies, it contains all the main food groups, ie, dairy, meat, fish, fruits, and vegetables, and a few food items that were culture dependent such as tofu and soy sauce. We did not record the portion size of intake.

The FFQ has been validated against 4 dietary recalls and a comprehensive FFQ in Argentina, Brazil, and Colombia (unpublished data; see Table II in the online-only Data Supplement) and has been found to be applicable to different countries despite regional differences in dietary constituents.[10] In the INTERHEART study, Iqbal et al[10] tested the reliability of the FFQ on 292 subjects and observed that the correlation coefficients for reliability of food items varied between 0.6 and 0.8. By using this FFQ, the INTERHEART study had previously identified some food items as risk factors for MI. These food items had been related to CVD risk in other studies, conferring face validity to the FFQ. For the present analyses, all frequencies of consumption were converted to times per day.

Assessment of Diet Quality

Dietary constituents and nutrients are not consumed in isolation, and the existence of correlation and interaction between nutrients may confound the diet-disease association. Recently, the association between chronic diseases and diet has been investigated by studying dietary patterns using 2 different approaches: a priori and a posteriori. These a priori and a posteriori approaches, as used in previous studies,[10–12] were used in this study to assess the association between diet quality and CVD events among high-risk individuals. The online-only Data Supplement contains methods and results for an a posteriori approach called the Diet Risk Score (DRS).

A Priori Dietary Pattern: Modified Alternative Healthy Eating Index

Our approach for measuring healthy eating was an adaptation of the Alternative Healthy Eating Index (AHEI) approach described by McCullough et al.[12] Because we measured intake of food items differently and portion sizes were not recorded by our FFQ, we used the frequency of consumption for our scoring system. In this study, we measured 7 of the 9 food items included in the AHEI; of these, 4 variables were identical (vegetables, fruits, nuts and soy proteins, and alcohol consumption) and 3 items were comparable (whole grains in place of cereal fiber, deep-fried foods in place of *trans* fats,[13] and the ratio of fish to meat plus eggs in place of the ratio of white to red meat). The scoring system for each food item was similar to that of the AHEI scoring system (Table III in the online-only Data Supplement). Higher scores indicated more frequent intake of healthy food such as vegetables and fruits and a higher intake of fish relative to meat, poultry, and eggs. We did not include multivitamins because few participants reported frequent use. For fiber intake, on the basis of the distribution of our cohort and assuming that each serving of whole grain contains 5 g fiber,[14] we assigned 10 points for ≥3 servings of whole grains and 0 points for no intake. Conversely, for deep-fried foods, the highest score was given for the lowest intake (10 points for ≤0.5 times a day and 0 points for ≥4 times a day). Because no portion sizes were assigned to our food items, we were unable to quantify daily intake of foods in grams and to compute daily nutrient intakes. Hence, we excluded the ratio of polyunsaturated fatty acids to saturated fatty acids. Finally, the points for each item for each participant were summed, and the total score was calculated. A healthy diet was indicated by better adherence to dietary recommendations and reflects a high intake of fruits, vegetables, whole grains, and nuts and a higher intake of fish relative to meat, poultry, and eggs.

Statistical Analysis

Means (SD) and medians were calculated to summarize continuous variables. Recorded frequencies of consumption were converted to daily intake, and scores were calculated. For the a priori approach, individuals were stratified separately into quintiles of modified AHEI (mAHEI) on the basis of total scores. For the a posteriori approach, 5 groups of DRSs were constructed by collapsing the 2 groups with scores of 0 and 1 into a single group. We grouped countries based on similarity of food habits and created regions as follows: all European and North American countries, Australia, and New Zealand were grouped as Western countries; South American countries included Argentina, Brazil, Chile, and Colombia; Eastern countries included China, Hong Kong, Philippines, Singapore, Malaysia, South Korea, Thailand, and Taiwan; and the small number of patients from Africa, United Arab Emirates, and Turkey were grouped with the Eastern countries.

Associations between the first occurrence of the primary outcome events and diet quality were assessed with Cox proportional hazard

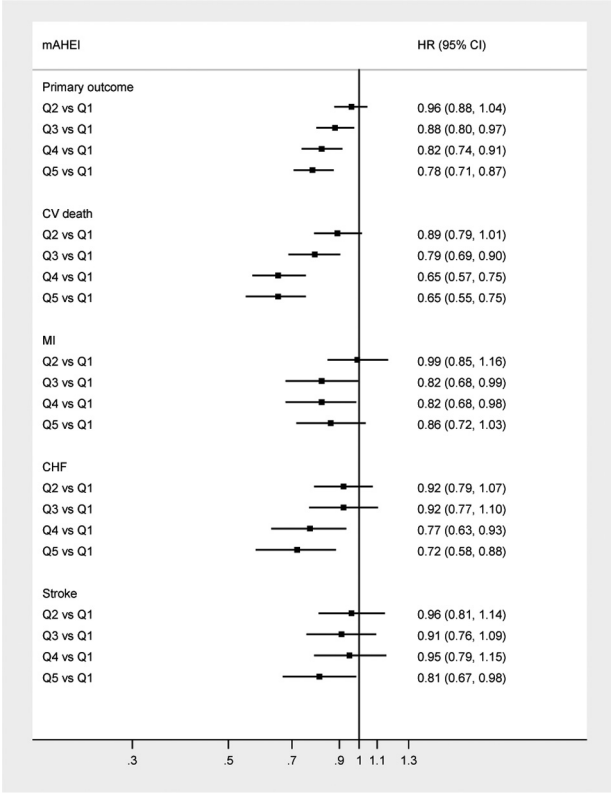


Figure 1. Hazard ratios (HRs) and 95% confidence intervals (CIs) of primary outcome and other major cardiovascular (CV) disease outcomes according to overall diet quality (modified Alternative Healthy Eating Index [mAHEI]; quintile [Q] 5 vs Q1, healthiest vs unhealthiest). All HRs are adjusted for age; sex; region; trial enrollment allocation; education; smoking; physical activity; body mass index (BMI); systolic and diastolic blood pressures; history of hypertension, diabetes mellitus, and stroke/transient ischemic attack; β-blockers; calcium channel blockers; antiplatelets; and statin. Categories of covariate adjustments were as follows. Regions: West region vs South America, East region vs South America. Medication: telmisartan vs placebo, ramipril vs placebo, combination vs placebo for Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET) and telmisartan vs placebo for Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects With Cardiovascular Disease (TRANSCEND). Education: 9 to 12 vs <8 years of education, trade/university vs <8 years of education. Smoking: current vs never smoker, former vs never smoker. Physical activity: moderate physical activity vs sedentary physical activity, rigorous physical activity vs sedentary physical activity. Continuous variables were blood pressure, BMI, waist circumference, and waist-to-hip ratio. Binary variables included history of stroke/transient ischemic attack, hypertension, diabetes mellitus; β-blocker intake; or use of diltiazem/verapamil. *P* for trend <0.001. MI indicates myocardial infarction; CHF, congestive heart failure.

Table 2. HRs and 95% CIs of Composite Outcome for Individuals With Different Types of Medication Use and Quintiles of Modified Alternative Healthy Eating Index (Quintile 5 Versus 1, Healthiest Versus Unhealthiest)

	mAHEI				*P* for Trend
	Q2 vs Q1	Q 3 vs Q1	Q4 vs Q1	Q5 vs Q1	
Aspirin use					
Yes (n=23 828)	0.96 (0.88–1.06)	0.86 (0.77–0.95)	0.80 (0.71–0.89)	0.79 (0.70–0.89)	<0.001
No (n=7718)	0.92 (0.78–1.08)	0.92 (0.78–1.10)	0.85 (0.71–1.02)	0.72 (0.60–0.87)	<0.001
β-blocker use					
Yes (n=18 036)	1.00 (0.89–1.12)	0.85 (0.75–0.96)	0.83 (0.72–0.95)	0.75 (0.66–0.87)	<0.001
No (n=13 510)	0.91 (0.80–1.02)	0.91 (0.80–1.04)	0.80 (0.70–0.92)	0.81 (0.71–0.93)	<0.001
Statin use					
Yes (n=19 055)	0.96 (0.86–1.07)	0.85 (0.74–0.97)	0.80 (0.70–0.92)	0.76 (0.66–0.87)	<0.001
No (n=12 491)	0.95 (0.83–1.07)	0.91 (0.80–1.04)	0.83 (0.72–0.96)	0.81 (0.71–0.94)	<0.001
Combination of any drugs					
Any 1 drug (n=28 721)*	0.95 (0.87–1.04)	0.86 (0.78–0.95)	0.81 (0.73–0.90)	0.77 (0.70–0.86)	<0.001
Any 2 drugs (n=11 192)	0.94 (0.82–1.08)	0.87 (0.75–1.00)	0.81 (0.70–0.94)	0.77 (0.65–0.90)	<0.001
Any 3 drugs (n=10 503)	1.02 (0.87–1.20)	0.84 (0.70–0.99)	0.79 (0.66–0.96)	0.77 (0.63–0.93)	<0.001

HR indicates hazard ratio; CI, confidence interval; mAHEI, modified Alternative Healthy Eating Index; and Q, quintile. All HRs are adjusted for age; sex; region; trial enrollment allocation; education; smoking; physical activity; body mass index; systolic and diastolic blood pressures; history of hypertension, diabetes mellitus, and stroke/transient ischemic attack; β-blockers; calcium channel blockers; antiplatelets; and statin. Categories of covariate adjustments were as follows. Regions: West region versus South America, East region versus South America. Medication: telmisartan versus placebo, ramipril versus placebo, combination versus placebo for Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET) and telmisartan versus placebo for Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects With Cardiovascular Disease (TRANSCEND). Education: 9 to 12 versus <8 years of education, trade/university versus <8 years of education. Smoking: current versus never smoker, former versus never smoker. Physical activity: moderate physical activity versus sedentary physical activity, rigorous physical activity versus sedentary physical activity. Continuous variables were blood pressure, body mass index, waist circumference, and waist-to-hip ratio. Binary variables included history of stroke/transient ischemic attack, history of hypertension, history of diabetes mellitus, β-blocker intake, and diltiazem/verapamil.

*In addition to angiotensin receptor blocker/angiotensin-converting enzyme drug use, which was used by all patients in ONTARGET and half the patients in TRANSCEND.

regression. Estimates of association were controlled for known potential risk factors for CVD. Among risk factors, we defined BMI and blood pressure as continuous variables and history of disease and medications as binary variables. Covariates of regions, education, smoking, and physical activity were classified as categorical variables. In a stepped approach in the first multivariable model, the risk of study outcome was controlled for age, sex, trial enrolled (ONTARGET or TRANSCEND), trial treatment allocation, and geographic region. In the second model, education, smoking, physical activity, and type of medication taken by individuals were added to the first model. The final model was further adjusted for BMI, blood pressure, history of hypertension, history of diabetes mellitus, cerebrovascular disease, coronary and peripheral artery disease, and all other cardiovascular medications.

To examine whether our findings differ across countries with various economic status, we grouped countries into middle and high income following the World Bank classification.[15] In addition, to account for intraclass correlations within centers, the standard error of coefficients was estimated from the robust sandwich approach. For each outcome of CV death, MI, CHF, stroke, non-CV hospitalization, fracture, injuries, and cancer, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated separately.

Further analyses were conducted for participants on effective drugs (aspirin, statins, and β-blockers) and for those not on these drugs. Because most patients were on angiotensin modulators that were used in the study, this association was not examined separately. We compared HRs among individuals who used any one, two, or three of these medications. In addition, the associations between diet quality and the primary outcome were assessed among patients with and without hypertension, diabetes mellitus, history of cerebrovascular disease, and coronary or peripheral artery disease.

Furthermore, Cox regressions were run for each dietary component of the dietary indexes and the primary outcome (Table IV in the online-only Data Supplement). We assessed the association between these 2 dietary indexes using the Spearman correlation coefficient. For all analyses, the criterion for statistical significance was set to $\alpha=0.05$. We used SAS version 8.2 (SAS Institute, Cary, NC) on a Unix operating system, and all figures were prepared with STATA version 11.0.

Results

The first of any one of the composite primary outcome events (composite of CV death, MI, stroke, or CHF) occurred in 4221 patients in ONTARGET and 969 in TRANSCEND. Altogether, there were 5190 primary outcomes (2271 CV deaths, 1554 MIs, 1395 strokes, and 1343 CHF) and 1524 new cancers.

Table 1 shows the distribution of patients' baseline characteristics by mAHEI. For mAHEI, those with higher diet quality were more likely to be older, were less likely to smoke, consumed more alcohol, were more active, and had a lower BMI ($P<0.001$ for all variables). Adherence to randomized medications and weight change during the study were similar among participants in all quintiles of mAHEI ($P>0.05$). The Spearman correlation coefficient between the 2 dietary indexes was 0.51 ($P<0.001$).

After adjusting for age, sex, trial enrollment, study medication allocation, and region, we observed that the risk of

Table 3. HRs and 95% CIs of the Composite Outcome for Individuals With Risk Factors or History of Diseases and According to Quintiles of the Modified Alternative Healthy Eating Index (Quintile 5 Versus 1, Healthiest Versus Unhealthiest)

	mAHEI				*P* for Trend
	Q2 vs Q1	Q3 vs Q1	Q4 vs Q1	Q5 vs Q1	
Hypertensive (n=26 307)	0.99 (0.91–1.08)	0.91 (0.83–1.01)	0.85 (0.77–0.95)	0.83 (0.74–0.92)	<0.0001
Normotensive (n=5239)	0.74 (0.58–0.95)	0.69 (0.53–0.88)	0.61 (0.47–0.78)	0.56 (0.42–0.74)	<0.0001
Diabetes mellitus, FPG ≥7 mg/dL (n=12 869)	0.96 (0.85–1.09)	0.91 (0.80–1.04)	0.86 (0.75–0.99)	0.75 (0.65–0.87)	<0.0001
No diabetes mellitus, FPG <7 mg/dL (n=18 676)	0.95 (0.84–1.07)	0.85 (0.74–0.96)	0.78 (0.69–0.90)	0.81 (0.71–0.92)	<0.0001
LDL median ≥2.80 mg/dL (n=15 254)	0.97 (0.87–1.09)	0.89 (0.79–1.00)	0.83 (0.73–0.95)	0.82 (0.72–0.94)	<0.001
LDL median <2.80 mg/dL (n=15 218)	0.94 (0.82–1.07)	0.87 (0.76–1.01)	0.82 (0.71–0.95)	0.76 (0.66–0.87)	<0.0001
With stroke/transient ischemic attack (n=6644)	0.94 (0.80–1.12)	0.82 (0.69–0.97)	0.79 (0.65–0.95)	0.78 (0.66–0.93)	<0.0001
Without stroke/transient ischemic attack (n=24 892)	0.96 (0.86–1.05)	0.90 (0.81–1.00)	0.83 (0.74–0.94)	0.78 (0.69–0.89)	<0.0001
With CAD (n=23 520)	0.97 (0.88–1.07)	0.85 (0.76–0.95)	0.83 (0.73–0.93)	0.78 (0.69–0.88)	<0.001
Without CAD (n=8026)	0.93 (0.77–1.12)	0.98 (0.83–1.16)	0.83 (0.69–0.99)	0.82 (0.69–0.98)	0.01
With PAD (n=4140)	0.92 (0.76–1.11)	1.02 (0.83–1.23)	0.77 (0.62–0.94)	0.92 (0.73–1.14)	0.1
Without PAD (n=27 406)	0.96 (0.88–1.06)	0.85 (0.77–0.95)	0.83 (0.74–0.93)	0.77 (0.68–0.86)	<0.0001

HR indicates hazard ratio; CI, confidence interval; mAHEI, modified Alternative Healthy Eating Index; Q, quintile. FPG, fasting plasma glucose; LDL, low-density lipoprotein; TIA, transient ischemic attacks; CAD, coronary artery disease; and PAD, peripheral artery disease. All HRs are adjusted for age; sex; region; trial enrollment allocation; education; smoking; physical activity; body mass index; systolic and diastolic blood pressures; history of hypertension, diabetes mellitus, and stroke/TIA; β-blockers; calcium channel blockers; antiplatelets; and statin. Categories of covariate adjustments were as follows. Regions: West region versus South America, East region versus South America. Medication: telmisartan versus placebo, ramipril versus placebo, combination versus placebo for Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET) and telmisartan versus placebo for Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects With Cardiovascular Disease (TRANSCEND). Education: 9 to 12 versus <8 years of education, trade/university versus <8 years of education. Smoking: current versus never smoker, former versus never smoker. Physical activity: moderate physical activity versus sedentary physical activity, rigorous physical activity versus sedentary physical activity. Continuous variables were blood pressure, body mass index, waist circumference, and waist-to-hip ratio. Binary variables included history of stroke/TIA, history of hypertension, diabetes mellitus, β-blocker intake, diltiazem/verapamil.

primary composite outcome demonstrated a graded and lower risk in the highest versus lowest mAHEI quintile (healthiest versus unhealthiest diet groups), with participants with the lowest scores used as the reference group. To further understand the association between overall diet quality and outcome, we conducted a model without potential mediators of dietary effects (such as BMI, waist-to-hip ratio, blood pressure, hypertension, history of diabetes mellitus, and stroke/transient ischemic attack). The observed inverse association remained significant (for primary outcome: HR, 0.76; 95% CI, 0.69–0.84; for CV death: HR, 0.63; 95% CI, 0.54–0.73; for MI: HR, 0.85; 95% CI, 0.71–1.02; for CHF: HR, 0.67; 95% CI, 0.54–0.82; and for stroke: HR, 0.81; 95% CI, 0.67–0.98, top versus lowest quintile of mAHEI; *P* for trend ≤0.001). These associations remained consistent after further adjustments for additional risk factors and all other medications that participants were taking (HR, 0.78; 95% CI, 0.71–0.87, top versus lowest quintile of mAHEI; *P* for trend ≤0.001; Figure 1). For each type of event, significant (*P*<0.001) inverse associations were observed when the highest mAHEI scores were compared with the lowest mAHEI scores; the reductions in risk for CV death, MI, CHF, and stroke were 35%, 14%, 28%, and 19%, respectively.

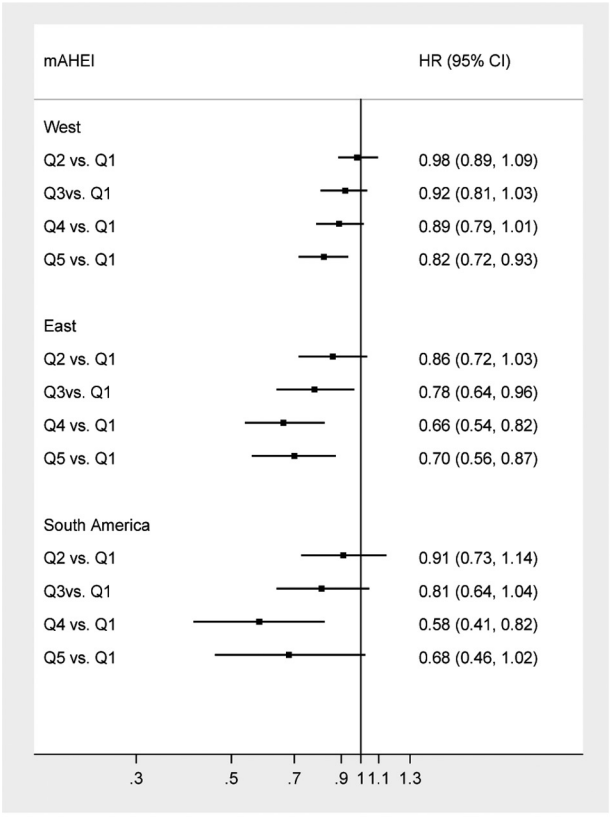
In an analysis of dietary components, we observed a modest but significantly reduced risk of primary outcome with increased consumption of vegetables, fruit, soy protein, and alcohol and an increased risk with greater intake of meat, poultry, and eggs (Table IV in the online-only Data Supplement).

The risk of ischemic stroke (n=1049) was inversely associated with mAHEI (*P* for trend=0.06). However, mAHEI did not predict hemorrhagic stroke (n=129, *P*=0.20) with or without adjustment for blood pressure.

The association of mAHEI with the primary outcome was evaluated in patients receiving aspirin (n=23 828), β-blockers (n=18 036), and statins (n=19 055) in Table 2 . The high-quality diet was associated with a consistent benefit regardless of these proven secondary prevention measures.

In subset analyses, higher diet quality was consistently associated with a lower risk of the primary outcome across the different categories of risk factors and comorbidities (Table 3). No significant association by risk factors was found.

Similar results were observed when the association between overall diet quality measured by DRS was assessed with primary outcome, each component of outcome, and



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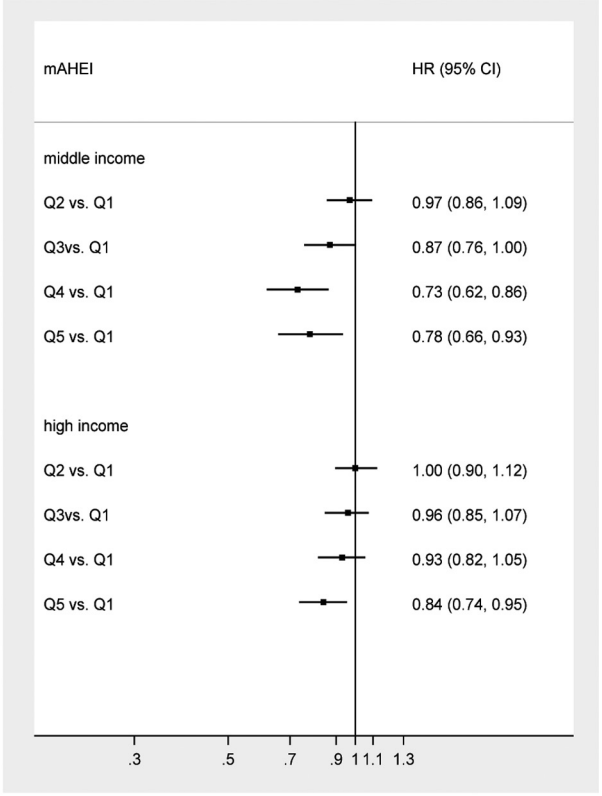

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Figure 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) of primary composite outcome associated with overall diet quality by (**A**) regions and (**B**) countries grouped by income (modified Alternative Healthy Eating Index [mAHEI]; quintile [Q] 5 vs Q1, healthiest vs unhealthiest). All HRs are adjusted for age; sex; region; trial enrollment allocation; education; smoking; physical activity; body mass index (BMI); systolic and diastolic blood pressures; history of hypertension, diabetes mellitus, and stroke/transient ischemic attack; β-blockers; calcium channel blockers; antiplatelets; and statin. Categories of covariate adjustments were as follows. Regions: West region vs South America, East region vs South America. Medication: telmisartan vs placebo, ramipril vs placebo, combination vs placebo for Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET) and telmisartan vs placebo for Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects With Cardiovascular Disease (TRANSCEND). Education: 9 to 12 years vs <8 years of education, trade/university vs <8 years of education. Smoking: current vs never smoker, former vs never smoker. Physical activity: moderate physical activity vs sedentary physical activity, rigorous physical activity vs sedentary physical activity. Continuous variables were blood pressure, BMI, waist circumference, and waist-to-hip ratio. Binary variables included history of stroke/transient ischemic attack, hypertension, or diabetes mellitus; β-blocker intake; and diltiazem/verapamil. *P* for trend for all regions <0.01.

different categories of risk factors and comorbidities (Tables V–VII in the online-only Data Supplement).

To determine whether geographical variation influences the relationship between diet and CV events, we assessed associations within 3 regional strata. The association between mAHEI scores and the risk of CV events was significant across the 3 regions (Figure 2A). After adjustment for all known confounding covariates, healthy eating was associated with a lower risk of composite of CV events by nearly 28% in Western countries, 30% in Eastern countries, and 32% in South American countries. To investigate the generalizability of our findings, we compared the results across countries grouped by income. Similar associations in both middle- and high-income countries were observed; healthy eating was associated with a lower risk of composite of CV events by nearly 22% in middle-income countries and 16% in high-income countries (Figure 2B). For DRS, we observed an ≈35% lower risk in all 3 regions (Figures I and II in the online-only Data Supplement).

Cancers, Non-CV Hospitalizations, Fractures, and Injuries

To assess the specificity of dietary impacts on CVD, we examined whether healthy eating was associated with other health outcomes, including non-CV hospitalization, cancer, fractures, and injuries. No significant association was found in multivariate analysis between mAHEI scores or DRS groups and cancer, fractures, or injuries (data not shown).

Discussion

In this study, we observed that diet quality in a large international cohort of individuals with known vascular disease or diabetes mellitus has a strong association with CVD outcomes. As far as we are aware, this is the first study to report the protective impact of healthy eating on CV death, new MI, stroke, and CHF events in patients taking secondary preventive drugs. The benefit of a high-quality diet was documented in high- and middle-income countries in different regions of the world.

We observed a graded association between diet quality and the recurrence of CVD events across all regions and various

income levels, even when applying 2 independent measures of diet quality, an a priori approach (mAHEI) and an a posteriori approach (DRS). Global application of the DRS has been examined previously,[10,16] whereas the AHEI was developed from dietary guidelines and used to assess the association of diet with major chronic disease in Western countries.[12,17] The present study modified and used this index globally and showed a protective impact of a healthy diet.

The clear associations of overall diet quality with risk for CVD, but not with cancer, fractures, injuries, and non-CV hospitalization, provide evidence for the specificity of diet on CVD risk and evidence that the associations we describe are not due to confounding by lifestyle factors or poor health. On the other hand, the people who follow a healthy diet may differ in ways we have not measured from those who do not, and our findings are suggestive but do not prove causality.

Our findings are consistent with several other studies using dietary indexes in major chronic diseases in primary prevention settings[18,19] and are compatible with the few existing studies that assessed the Mediterranean diet, diet quality, and the secondary prevention of CV events,[4,19,20] albeit in single geographic regions. In these studies, multiple mechanisms have been postulated to play a role in the protective effect of a high-quality diet; these include consumption of a broad range of nutrients such as potassium[21] and omega-3 fatty acid[22] and their beneficial effects on CV risk factors,[23–25] inflammatory processes, and oxidative stress, although definitive proof for the role of these mechanisms is lacking. However, evidence increasingly supports the view that a nutrient-based approach may be less helpful or even misleading for setting dietary guidelines to prevent chronic diseases because we do not consume food in isolation.[26]

We assessed the association of diet in addition to the proven drugs in secondary prevention and found a consistent beneficial association regardless of the type or combination of medication on the CVD outcomes. From this, we can infer that patients may derive an additive benefit when dietary modification is combined with proven drug therapies and other lifestyle changes.[3] This was also shown in patients with diabetes mellitus, in whom the risk reduction in CVD events with high-quality diets was similar to the effects of drug therapy.[24]

The main strength of our study is that it is the first to address very important questions using methodologically robust but simple measures of diet. The large number of patients with relatively long follow-up, the large number of events (>5000 CVD events), the international distribution of the cohort, the high completeness of the data, and the availability of detailed covariates that could be used to adjust for a broad range of potential confounders are added strengths. To the best of our knowledge, the present study represents the largest cohort of people with CV events and estimates of overall diet quality in different regions of the world, and we were able to demonstrate the impact of a high-quality diet in these different regions.

A major limitation is that the study was an observational study, so residual confounding cannot be entirely ruled out, despite adjustment for numerous potential confounders in multivariable models. Participants with severe disease at baseline may have opted to modify their diet. However, changes in diet over time would generally attenuate the results toward the null in prospective studies such as this study, and it is more likely to dilute than to strengthen the observed associations, so the true impact might be larger. In addition, after stratification analyses by use of medication and adjustment for modifiable risk factors, the parameter estimates remained strong. Our estimates are not adjusted for energy intake but are adjusted for BMI and physical activity, which are closely related to energy balance.[19,27,28] The FFQ was a qualitative questionnaire that has not been validated in all regions of the world; however, the success of prediction and the consistency of its finding with known protective factors of CVD suggest that this short questionnaire captured important food items. Consumption of some food items such as dairy, tofu, and soy sauce varies largely among countries. However, the assessment of diet quality in our study was not influenced by those variations because those food items were not components of DRS or mAHEI. Similar to other studies, we used short FFQs to assess the diet-disease relationship.[29] We acknowledge some inherent weaknesses of short FFQs, and it is likely that the diagnostic accuracy increases by expansion of the food list, although the clinical usefulness of FFQ designed for an international study was an important factor for our study. The decision to use a short FFQ was based on the realization that our study participants were older adults and that using a more comprehensive FFQ would likely introduce considerable burden and affect the response rate and reliability of answers because older adults are more likely to be frustrated or fatigued by lengthy questionnaires.[30]

Conclusions

Higher diet quality is associated with a lower risk of recurrent or new CVD events in individuals with prior CVD or diabetes mellitus with end-organ damage both in the overall population and in separate regions of the world. These associations were observed in people receiving proven drug therapies for secondary prevention, suggesting that dietary modification may have benefits in addition to those seen with aspirin, angiotensin modulators, lipid-lowering agents, and β-blockers. Highlighting the importance of healthy eating by health professionals and advising high-risk individuals to improve their diet quality would substantially reduce CVD recurrence beyond drug therapy alone and save lives globally.

Sources of Funding

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Disclosures

Drs Sleight, Dagenais, Probstfield, Teo, and Yusuf received grants, honoraria, consulting, lecture fees, or research grants from Boehringer Ingelheim and from other companies manufacturing angiotensin receptor blockers. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Although healthy diets have been shown to be associated with a lower risk of cardiovascular disease (CVD) in populations without prior CVD, much less is known about those with established CVD. We studied the association between overall diet quality and the recurrence of CVD among 31 546 individuals (age, 66.5± 6.2 years) with a history of CVD enrolled in 2 randomized trials, the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET) and the Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects With Cardiovascular Disease (TRANSCEND), from 40 middle- and high-income countries. A healthy diet consisted of high intake of fruits, vegetables, whole grains, nuts, and fish relative to meat and eggs. A graded association between diet quality and recurrence of CVD events across all regions and various income levels and across different categories of risk factors and comorbidities was observed. These associations were observed in people receiving proven drug therapies for secondary prevention, suggesting that the benefits of dietary modifications were in addition to those from the medications. These data suggest that at least 20% recurrence of CVD could be avoided by adhering to a healthy diet. Highlighting the importance of healthy eating by health professionals and advising high-risk individuals to improve their diet quality would substantially reduce CVD recurrence beyond drug therapy alone and save lives globally.

Relationship Between Healthy Diet and Risk of Cardiovascular Disease Among Patients on Drug Therapies for Secondary Prevention: A Prospective Cohort Study of 31 546 High-Risk Individuals From 40 Countries

Mahshid Dehghan, Andrew Mente, Koon K. Teo, Peggy Gao, Peter Sleight, Gilles Dagenais, Alvaro Avezum, Jeffrey L. Probstfield, Tony Dans and Salim Yusuf
on Behalf of the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET)/Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects With Cardiovascular Disease (TRANSCEND) Trial Investigators

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SUPPLEMENTAL MATERIAL

Supplemental Table 1 Description of food groups in the food group frequency questionnaire

a) Meat/poultry:	Includes beef, pork, lamb, mutton, goat, veal, rabbit, chicken, turkey, duck, pheasant; their curries; Mexican meat soups/stews (menudo), liver, kidney, brain, spleen, heart and sausages.
b) Fish:	Includes fresh-water and sea-water fish; preserved fish such as salted fish, canned fish, dried fish; shellfish and crustaceans (clams, squid, prawns, mollusks); caviar.
c) Eggs:	Includes preserved eggs, duck eggs, thousand year old eggs.
d) Whole grains:	Includes whole wheat flour; whole wheat chapatti, cracked wheat; brown/wild rice; corn/hominy/masa harina/corn flour/maize, oats - old fashioned & Scotch/cracked oats; couscous; pot barley, brown rusk; whole wheat pasta, semolina.
e) Refined grains:	Includes white flour; white flour chapatti; white/polished/instant/ parboiled rice; jook or rice congee; pasta; noodles/ramen/somen; bulgur; pearl barley, sago; plain rusk; sheermal; taftan.
f) Dairy products:	Includes milk, yogurt, cheese, curd, raita, lassi, custard, khoya, firni, kheer, milk puddings, and ice cream.
g) Deep fried foods:	Includes French fries, potato chips, onion rings, samosas, papad, pakoras; sev; fried won ton, egg roll.
h) Soy and other sauces:	Includes fish sauce, oyster sauce, tamari; fermented bean pastes (hoi sin); other salty sauces.
i) Salty snacks:	Includes salt added in cooking and to food at the table and salty snacks such as chips, crackers etc.
j) Pickled vegetables (brine):	Includes pickled in brine such as dill pickles, relishes; olives; salted cabbage or leafy greens (mui choi); mango pickle, lemon pickle; salted root vegetables (choi po); pickled eggs, pickled meat.
k) Desserts/sweet snacks:	Includes the use of jam; cakes; pies; chocolate; candy; burfi/ladoo; rasgulla/gulab jamun; halwa; shameia, mohalabeia, Chinese sweet buns; nor mei; sweet bean desserts, Coke and other soft drinks.
l) Sugar/sweetener:	Includes the use of white sugar, brown sugar, corn syrup, honey, molasses, maple syrup, treacle.
m) Tofu/soybean curd:	Includes textured vegetable protein, soy milk.
n) Legumes:	Includes dried beans, lentils, peas, daals; soups (split pea).

o) Nuts/seeds: Includes peanuts, almonds, sunflower seeds, cashews, walnuts.

p) Fruit: Includes all fruits

q) Fruit juice: include all types of natural fruit juice

r) Leafy greens vegetable: Includes all fresh leafy green vegetables: spinach, bok choi; choi sum, collards, mustard or turnip greens; asparagus.

s) Other raw vegetables: Includes any raw vegetables not included in the preceding categories.

t) Other cooked vegetables: Includes any cooked vegetables not included in the preceding categories.

Validation of Qualitative Food Frequency Questionnaire among Argentinean adults

Supplemental Table 2 de-attenuated correlation coefficients between daily consumption of selected food groups estimated by qualitative FFQ vs. mean of four 24DRs and cross-classifications into same and extreme quartiles of intake by two methods (n=74)

Food groups	De-attenuated Pearson correlation	Extreme quartiles (%)	Same quartiles (%)
Meat	0.58	32.0	68.0
Eggs	0.39	35.0	65.0
Whole grain	0.32	57.0	44.0
Refined grain	0.53	28.0	72.0
Fried food	0.43	40.0	60.0
Dessert	0.36	30.0	70.0
Sugar	0.72	24.0	76.0
Nuts	0.17	23.0	77.0
Fruit	0.47	19.0	81.0
Green leaf vegetables	0.39	27.0	73.0
Raw vegetables	0.56	30.0	70.0

Supplemental Table 3 modified Alternative Healthy Eating Index (mAHEI) scoring system

Food items	**Criteria for minimum score of 0**	**Criteria for maximum score of 10**
Fruits (serving/d)	0	4
Vegetables (serving/d)	0	5
Nuts and soy protein (serving/d)	0	1
Ratio of fish/(meat + eggs)	0	4
Whole grain (serving/d)	0	≥3
Fried foods (serving/d)	≥4	≤0.5
Alcohol (serving/d)	Men: 0 or > 3.5	Men: 1.5-2.5
	Women: 0 or > 2.5	Women: 0.5-1.5
Total score of participants	3.1	66.7

Assessment of diet quality

***A posteriori* dietary pattern: the Diet Risk Score (DRS)**

Sullivan et al.[1] developed a point system to create the Framingham study risk score and Iqbal et al.[2] utilized the point system and created the DRS which was used in the INTERHEART [2] and INTERSTROKE [3] studies. The INTERHEART study identified fruits, green leafy vegetables, other raw vegetables, and other cooked vegetables as protective, but meat, salty snacks, and fried foods harmful for MI. We followed the INTERHEART methodology and identified food items to create the DRS based on our study sample. We conducted a cox regression model with protective and harmful food items, age, sex and region and calculated the parameter of estimate ($ß_i$). Frequency of consumption of food items (continuous variables) were divided into quartiles, with the reference values as the mid points of the quartiles, denoted by $\mathbf{W_{ij}}$. For the binary variable, sex, the reference was female. The constant ß (as in Sullivan et al.) was based on age "with the increase in risk associated with a 5years increase in age" (i.e. $B= ß_{age} * 5$). For each of the risk factors, the base category was the least risky category; reference of the base category was denoted by $\mathbf{W_{iREF}}$**.** The points for the food items were then determined by the formula: $Points_{ij}=ß_i(W_{ij}- W_{iREF})/B$. Our final model identified fruit, green vegetable, and raw vegetable as protective and meat as harmful food items. None of the other food items were significantly associated with the outcome variable. Then the scores for all significant food items were summed up to form the total score. There were six groups in the DRS and participants' final score varied from zero (unhealthiest diet) to five (healthiest). Five groups of DRS were constructed by collapsing the two groups with scores of zero and one into a single group.

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Results

Supplemental Table 4 Hazard Ratio (HR) of primary outcome for each component of modified Alternative Healthy Eating Index (mAHEI) and Diet Risk Score (DRS)

	mAHEI		DRS	
Food items	HR (95%CI)	P	HR (95%CI)	P
All types of vegetables (serving/d)	0.98 (0.97-1.00)	0.02	NI	__
Green leafy vegetables (serving/d)	NI	___	0.93 (0.89-0.97)	<0.001
Other raw vegetables (serving/d)	NI	___	0.89 (0.84-0.94)	<0.001
Other cooked vegetables (serving/d)	NI	___	0.98 (0.94-1.02)	0.30
Fruit/fruit juice (serving/d)	0.97 (0.95-0.99)	<0.001	0.94 (0.91-0.97)	<0.001
Soy protein /nuts (serving/d)	0.91 (0.86-0.97)	<0.001	NI	__
Fish (serving/d)	0.96 (0.90-1.02)	0.20	NI	__
Meat, poultry and eggs (serving/d)	1.03 (1.02-1.05)	<0.001	1.06 (1.01-1.11)	0.01
Ratio fish/(meat, poultry, eggs)	1.00 (0.99-1.01)	0.80	NI	__
Fried food (serving/d)	1.07 (0.99-1.16)	0.10	1.11 (0.98-1.26)	0.10
Salty food and snacks (serving/d)	NI	___	0.95 (0.90-1.01)	0.12
Alcohol (serving/d)	0.90 (0.87-0.93)	<0.001	NI	__

NI: Not included in that specific index

Supplemental Table 5 Baseline characteristics of participants according to groups of Diet Risk Score (DRS) (D1 unhealthiest, D5 healthiest)

Variable	**D1**	**D2**	**D3**	**D4**	**D5**
	n=8790	n=8567	n=7785	n=4127	n=1344
Age mean (SD)	66.0 (7.2)	66.7 (7.2)	66.7 (7.2)	66.6 (7.3)	66.8 (7.3)
Education n (%)					
Up to high school	5636 (64.1)	5474 (63.9)	4895 (62.9)	2562 (62.0)	839 (62.4)
Trade school, college, university	3153 (35.9)	3093 (36.1)	2890 (37.1)	1565 (38.0)	504 (37.6)
Current Smoke, yes n (%)	1532 (17.4)	1016 (11.9)	726 (9.3)	333 (8.1)	86 (6.4)
Alcohol use, yes n (%)	3390 (38.6)	3248(37.9)	2975 (38.2)	1652 (40.0)	498 (37.1)
*Adhered to medication n (%)	5831 (66.4)	5776 (67.4)	5172 (66.5)	2707 (65.6)	913 (67.9)
Physical activity (%)					
2-4 times/wk n (%)	2103 (23.9)	1986 (23.2)	1661 (21.3)	905 (21.9)	291 (21.7)
5-6 times/ wk n (%)	652 (7.4)	632 (7.4)	554 (7.1)	363 (8.8)	106 (7.9)
BMI mean (SD)	28.3 (4.6)	27.9 (4.5)	28.0 (4.5)	28.1 (4.5)	28.3 (4.5)
†Gained weight n (%)	3079 (46.4)	3183 (47.5)	2814 (46.9)	1512 (47.0)	536 (48.1)

*p for trends for adherence to medication (yes %) was 0.78 for DRS groups
† p for trends for weight gain was 0.2 for DRS groups

Supplemental Table 6 HR and 95% CI of composite outcome for individuals with different types of medication use and the groups of Diet Risk Score (D5 vs. D1 healthiest vs. unhealthiest)

	Groups of DRS				
	D2 vs. D1	**D 3 vs. D1**	**D4 vs. D1**	**D5 vs. D1**	**P trend**
Aspirin use					
Yes (n=23828)	0.93 (0.85-1.01)	0.91 (0.83-0.99)	0.88 (0.78-0.99)	0.59 (0.48-0.73)	<0.001
No (n= 7718)	0.99 (0.85-1.15)	1.04 (0.88-1.22)	0.87(0.73-1.04)	0.78 (0.57-1.05)	0.10
Beta-blockers use					
Yes (n=18036)	0.97(0.87-1.07)	0.94 (0.84-1.04)	0.94 (0.83-1.07)	0.53(0.41-0.68)	<0.001
No (n=13510)	0.91(0.81-1.03)	0.94 (0.83-1.07)	0.81(0.70-0.95)	0.77(0.60-0.97)	0.003
Statin use					
Yes (n=19055)	0.90 (0.80-1.00)	0.89 (0.79-1.00)	0.87(0.76-1.00)	0.60 (0.47-0.75)	<0.001
No (n=12491)	1.01 (0.90-1.13)	1.01 (0.89-1.14)	0.88 (0.76-1.02)	0.71 (0.54-0.93)	0.03
Combination of any drugs					
*Any one drug (n=28721)	0.96 (0.88-1.04)	0.92 (0.85-1.01)	0.89 (0.81-0.99)	0.60 (0.50-0.73)	<0.001
Any two drugs (n=11192)	0.93 (0.82-1.06)	0.85(0.75-0.97)	0.89 (0.75-1.04)	0.53(0.39-0.72)	<0.001
Any three drugs (n=10503)	0.89 (0.77-1.02)	0.92 (0.80-1.06)	0.90 (0.76-1.08)	0.57 (0.41-0.79)	0.01

*In addition to ARB/ACE drug use, which was used by all patients in ONTARGET and half the patients in TRANSCEND

Abbreviations: HR, hazard ratio; DRS, diet risk score.

All HRs are adjusted for age, sex, region, trial enrolment allocation, education, smoking, physical activity, BMI, systolic and diastolic blood pressure, history of hypertension, diabetes and stroke/TIA, beta-blockers, CCB, Anti-platelets and statin.

Categories of covariate adjustments were as: Regions: West region vs. South America, East region vs. South America. Medication: Telmisartan vs. placebo, Ramipril vs. placebo, Combination vs. placebo for ONTARGET and Telmisartan vs. placebo or TRANSCEND. Education: 9-12years vs. <8 years education, trade/university vs. <8 years education. Smoking: Current vs. never smoker, former vs. never smoker. Physical activity: moderate physical activity vs. sedentary physical activity, rigorous physical activity vs. sedentary physical activity. Continuous variables were blood pressure, BMI, waist and waist/hip ratio. Binary variables include; History of stroke/TA, history of hypertension, diabetes, Beta-blocker intake, Diltiazem / Verapamil.

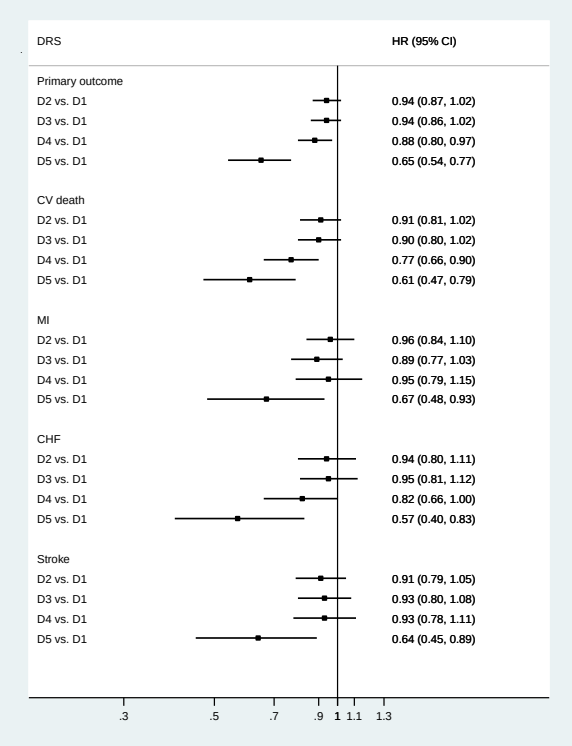
Supplemental Table 7 HR and 95% CI of composite outcome for individuals with risk factors or history of diseases and the groups of Diet Risk Score (D5 vs. D1 healthiest vs. unhealthiest)

	Groups of DRS				
	D2 vs. D1	**D3 vs. D1**	**D4 vs. D1**	**D5 vs. D1**	**P trend**
Hypertensive (n=26307)	0.97 (0.89-1.06)	0.97 (0.88-1.06)	0.92 (0.82-1.02)	0.65(0.54-0.79)	<0.001
Normotensive (n=5239)	0.78 (0.64-0.96)	0.79 (0.64-0.97)	0.68(0.52-0.90)	0.59 (0.39-0.91)	<0.001
Diabetes FPG >=7 (n=12869)	0.92 (0.79-1.06)	0.89 (0.77-1.04)	0.94 (0.79-1.12)	0.67(0.48-0.92)	0.06
No Diabetes FPG <7 (n=18676)	0.98 (0.89-1.09)	0.96 (0.86-1.07)	0.85(0.74-0.98)	0.65(0.52-0.83)	<0.001
LDL median ≥ 2.80 (n=15254)	0.95(0.85-1.05)	0.96 (0.86-1.07)	0.87(0.76-1.00)	0.73(0.58-0.91)	0.001
LDL median < 2.80 (n= 15218)	0.96 (0.85-1.08)	0.95(0.84-1.07)	0.92 (0.79-1.06)	0.60 (0.46-0.78)	0.003
With Stroke/TIA (n= 6644)	1.01(0.87-1.18)	0.99 (0.84-1.16)	0.98 (0.82-1.17)	0.70 (0.49-1.00)	0.20
Without stroke/TIA (n=24892)	0.92 (0.84-1.01)	0.93(0.84-1.02)	0.85 (0.76-0.96)	0.63 (0.51-0.76)	<0.001
With CAD (n = 23520)	0.94 (0.86-1.02)	0.94 (0.85-1.03)	0.88 (0.79-0.99)	0.62 (0.50-0.76)	<0.001
Without CAD (n= 8026)	0.98 (0.84-1.15)	0.96 (0.80-1.15)	0.90 (0.75-1.09)	0.77 (0.54-1.10)	0.13
With PAD (n =4140)	0.90 (0.77-1.06)	0.84 (0.69-1.02)	0.77(0.61-0.99)	0.69 (0.46-1.02)	0.006
Without PAD (n = 27406)	0.95(0.87-1.04)	0.96(0.88-1.06)	0.91(0.81-1.01)	0.64 (0.53-0.77)	<0.001

Abbreviations: HR, hazard ratio; DRS, diet risk score; FPG, fasting plasma glucose; LDL, low density lipoprotein; TIA, transient ischemic attacks; CAD, coronary artery disease; PAD, peripheral artery disease; CCB, calcium

All HRs are adjusted for age, sex, region, trial enrolment allocation, education, smoking, physical activity, BMI, systolic and diastolic blood pressure, history of hypertension, diabetes and stroke/TIA, beta-blockers, CCB, Anti-platelets and statin.

Categories of covariate adjustments were as: Regions: West region vs. South America, East region vs. South America. Medication: Telmisartan vs. placebo, Ramipril vs. placebo, Combination vs. placebo for ONTARGET and Telmisartan vs. placebo or TRANSCEND. Education: 9-12years vs. <8 years education, trade/university vs. <8 years education. Smoking: Current vs. never smoker, former vs. never smoker. Physical activity: moderate physical activity vs. sedentary physical activity, rigorous physical activity vs. sedentary physical activity. Continuous variables were blood pressure, BMI, waist and waist/hip ratio. Binary variables include; History of stroke/TA, history of hypertension, diabetes, Beta-blocker intake, Diltiazem / Verapamil.



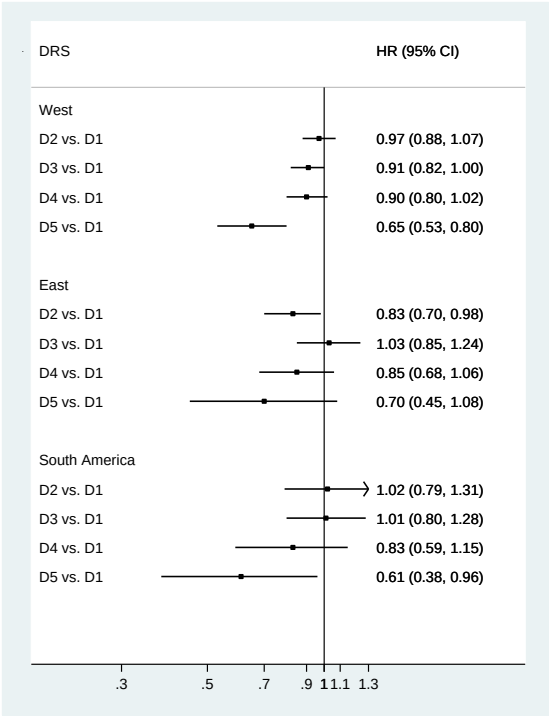
Supplemental Figure 1 Hazard Ratio (HR) and 95% CI of primary outcome and other major CVD outcomes according to overall diet quality (DRS D5 vs. D1, healthiest vs. unhealthiest). p for trend <0.001.

Abbreviations: HR, hazard ratio; DRS diet risk score; MI, myocardial infarction; CHF, congestive heart failure.

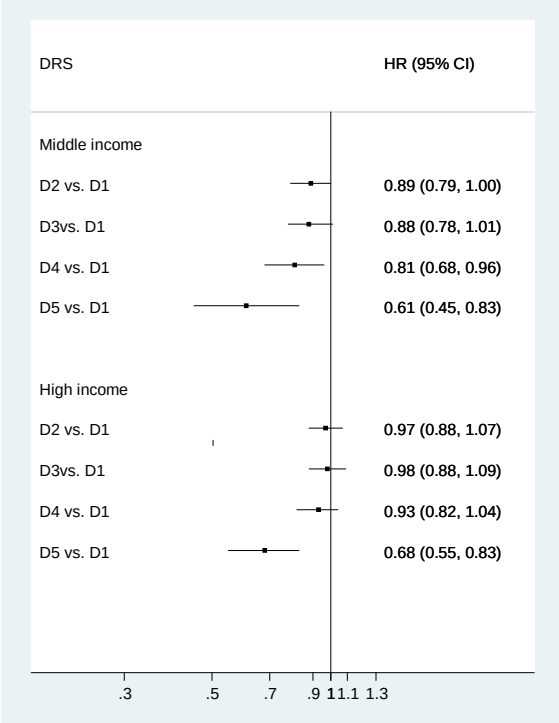
All HRs are adjusted for age, sex, region, trial enrolment allocation, education, smoking, physical activity, BMI, systolic and diastolic blood pressure, history of hypertension, diabetes and stroke/TIA, beta-blockers, CCB, Anti-platelets and statin.

Categories of covariate adjustments were as: Regions: West region vs. South America, East region vs. South America. Medication: Telmisartan vs. placebo, Ramipril vs. placebo, Combination vs. placebo for ONTARGET and Telmisartan vs. placebo or TRANSCEND. Education: 9-12years vs. <8 years education, trade/university vs. <8 years education. Smoking:

Current vs. never smoker, former vs. never smoker. Physical activity: moderate physical activity vs. sedentary physical activity, rigorous physical activity vs. sedentary physical activity. Continuous variables were blood pressure, BMI, waist and waist/hip ratio. Binary variables include; History of stroke/TA, history of hypertension, diabetes, Beta-blocker intake, Diltiazem / Verapamil


DRS
HR (95% CI)
West
D2 vs. D1
0.97 (0.88, 1.07)
D3 vs. D1
0.91 (0.82, 1.00)
D4 vs. D1
0.90 (0.80, 1.02)
D5 vs. D1
0.65 (0.53, 0.80)
East
D2 vs. D1
0.83 (0.70, 0.98)
D3 vs. D1
1.03 (0.85, 1.24)
D4 vs. D1
0.85 (0.68, 1.06)
D5 vs. D1
0.70 (0.45, 1.08)
South America
D2 vs. D1
1.02 (0.79, 1.31)
D3 vs. D1
1.01 (0.80, 1.28)
D4 vs. D1
0.83 (0.59, 1.15)
D5 vs. D1
0.61 (0.38, 0.96)
.3
.5
.7
.9
1
1.1
1.3

a


DRS
HR (95% CI)
Middle income
D2 vs. D1
0.89 (0.79, 1.00)
D3vs. D1
0.88 (0.78, 1.01)
D4 vs. D1
0.81 (0.68, 0.96)
D5 vs. D1
0.61 (0.45, 0.83)
High income
D2 vs. D1
0.97 (0.88, 1.07)
D3vs. D1
0.98 (0.88, 1.09)
D4 vs. D1
0.93 (0.82, 1.04)
D5 vs. D1
0.68 (0.55, 0.83)
.3
.5
.7
.9
1
1.1
1.3

b

Supplemental Figure 2 Hazard Ratio and 95% CI of primary composite outcome associated with ovearll diet quality a. regions and b. countries grouped by income (DRS, D5 vs. D1, healthiest vs. unhealthiest). P for trend for all regions were <0.01.

Abbreviations: HR, hazard ratio

All HRs are adjusted for age, sex, region, trial enrolment allocation, education, smoking, physical activity, BMI, systolic and diastolic blood pressure, history of hypertension, diabetes and stroke/TIA, beta-blockers, CCB, Anti-platelets and statin.

Categories of covariate adjustments were as: Regions: West region vs. South America, East region vs. South America. Medication: Telmisartan vs. placebo, Ramipril vs. placebo, Combination vs. placebo for ONTARGET and Telmisartan vs. placebo or TRANSCEND. Education: 9-12years vs. <8 years education, trade/university vs. <8 years education. Smoking: Current vs. never smoker, former vs. never smoker. Physical activity: moderate physical activity vs. sedentary physical activity, rigorous physical activity vs. sedentary physical activity. Continuous variables were blood pressure, BMI, waist and waist/hip ratio. Binary variables include; History of stroke/TA, history of hypertension, diabetes, Beta-blocker intake, Diltiazem / Verapamil.