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Population-Attributable Fractions of Modifiable Lifestyle Factors for CKD and Mortality in Individuals With Type 2 Diabetes: A Cohort Study

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Background: We quantified the impact of lifestyle and dietary modifications on chronic kidney disease (CKD) by estimating population-attributable fractions (PAFs).

Study Design: Observational cohort study.

Setting & Participants: Middle-aged adults with type 2 diabetes but without severe albuminuria from the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET; n = 6,916).

Factors: Modifiable lifestyle/dietary risk factors, such as physical activity, size of social network, alcohol intake, tobacco use, diet, and intake of various food items.

Outcomes: The primary outcome was CKD, ascertained as moderate to severe albuminuria or ≥5% annual decline in estimated glomerular filtration rate (eGFR) after 5.5 years. The competing risk for death was considered. PAF was defined as the proportional reduction in CKD or mortality (within 5.5 years) that would occur if exposure to a risk factor was changed to an optimal level.

Results: At baseline, median urinary albumin-creatinine ratio and eGFR were 6.6 (IQR, 2.9-25.0) mg/mmol and 71.5 (IQR, 58.1-85.9) mL/min/1.73 m^2, respectively. After 5.5 years, 704 (32.5%) participants developed albuminuria, 1,194 (55.2%) had a ≥5% annual eGFR decline, 267 (12.3%) had both, and 1,022 (14.8%) had died. Being physically active every day has PAFs of 5.1% (95% CI, 0.5%-9.6%) for CKD and 12.3% (95% CI, 4.9%-19.1%) for death. Among food items, increasing vegetable intake would have the largest impact on population health. Considering diet, weight, physical activity, tobacco use, and size of social network, exposure to less than optimum levels gives PAFs of 13.3% (95% CI, 5.5%-20.9%) for CKD and 37.5% (95% CI, 27.8%-46.7%) for death. For the 17.8 million middle-aged Americans with diabetes, improving 1 of these lifestyle behaviors to the optimal range could reduce the incidence or progression of CKD after 5.5 years by 274,000 and the number of deaths within 5.5 years by 405,000.

Limitations: Ascertainment of changes in kidney measures does not precisely match the definitions for incidence or progression of CKD.

Conclusions: Healthy lifestyle and diet are associated with less CKD and mortality and may have a substantial impact on population kidney health.

INDEX WORDS: Chronic kidney disease (CKD); renal function; albumin-creatinine ratio (ACR); disease progression; type 2 diabetes mellitus; diet; physical activity; lifestyle; healthy behavior; mortality; population attributable fraction (PAF); modifiable risk factor; public health recommendations; disease prevention.

Editorial, p. 1

Type 2 diabetes mellitus has been diagnosed in 8.3% of adults worldwide. In the United States, estimates of lifetime risk for diagnosed diabetes for adults are 40%.[1,2] Early chronic kidney disease (CKD) affects far more individuals and increases the risk for cardiovascular disease, 2 facts that have been ignored for a long time.[3-5] In the presence of CKD, worse prognosis has been found for diabetes and other acute and chronic disorders.[5] Hence, CKD is a risk

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[*]A list of participating ONTARGET Investigators appears in this article's online supplementary material (Item S1).

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factor for cardiovascular disease and a burden to health systems. An appealing approach may be to encourage individuals to follow a healthy lifestyle because comprehensive lifestyle interventions have been shown to be medically effective.[6,7]

In 2 studies,[8,9] we have evaluated associations of modifiable lifestyle and dietary risk factors with the incidence or progression of CKD and with mortality for individuals with type 2 diabetes using data from the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET)[10-12]: individuals with a healthier diet (modified Alternate Healthy Eating Index, mAHEI),[13,14] physically active individuals, individuals with a larger social network (social network score),[9] or individuals with moderate alcohol intake exhibited lower risk for CKD and mortality.

Here, we estimated population-attributable fractions (PAFs),[15] defined as the proportion of CKD or mortality cases that are attributable to a modifiable unhealthy lifestyle or dietary risk factor. Thus, PAF quantifies the proportion of CKD cases or deaths that could have been avoided by a healthier lifestyle. PAFs can be computed for various lifestyle factors by comparing the observed number of CKD cases or deaths with the hypothetical numbers that would have resulted if individuals had adhered to a healthier lifestyle. Hence, benefits of lifestyle modification can be compared quantitatively across different aspects of lifestyle. Numerically, the PAF of a specific risk factor combines into a single number the etiologic effect size of the risk factor on the outcome, the prevalence of unhealthy lifestyle (unfavorable exposure to the risk factor), and an assumed reduction in that prevalence. Hence, PAF analysis can reveal that a rare risk factor with a strong effect may be responsible for only a few CKD cases in a population, whereas a common risk factor with a weak effect can cause many CKD cases. The PAF measures the total effects of a risk factor (direct and mediated through other factors). Therefore, it can be used to assess the potential impact of preventive interventions on population health; for example, for the United States, one can estimate how many CKD cases in the approximately 17.8 million individuals (in 2012) 45 years or older with diagnosed diabetes are attributable to poor lifestyle behaviors.[2] Although improvements in lifestyle might not substantially change CKD prognosis for one person, improvements in lifestyle due to a prevention program can have noticeable consequences on a population level. Because randomized trials of lifestyle interventions for CKD are unlikely to be forthcoming, analysis of thoroughly collected observational data may give important clues to what extent CKD and mortality may be attributable to lifestyle interventions in a population of individuals with diabetes. Especially in cancer research, many studies have quantified the impact of modifiable lifestyle factors on cancer load, and PAF has been noted as a useful epidemiologic metric to develop effective prevention strategies by concentrating on the most influential modifiable factors.[16-20]

In this post hoc analysis, we quantifed PAFs for immediately modifiable personal behaviors of lifestyle and diet, including the mAHEI, body mass index (BMI), physical activity, social network score, consumption of alcohol, and tobacco use. Furthermore, we evaluated intake of vegetables, fruits, proteins, high-carbohydrate foods, and fried foods and urinary potassium and sodium. These results may guide public health recommendations for individuals with diabetes with the aim to reduce the incidence or progression of CKD and mortality and may help in prioritizing strategies to improve lifestyle.

METHODS

Study Design and Population

ONTARGET (ClinicalTrials.gov study number NCT00153101) randomly assigned 25,620 participants (aged ≥ 55 years) with vascular disease or type 2 diabetes with end-organ damage to receive telmisartan, ramipril, or both.[10] The trial was approved by the Research Ethics Board of Hamilton Health Sciences (#01-252). Written informed consent was obtained from all participants. We included all 6,916 participants with diabetes, no or moderate albuminuria at baseline, and information for confounders and the outcome (Fig S1, available as online supplementary material).

Selection of Modifiable Risk Factors

Risk factors for CKD were obtained once at baseline and encompassed BMI, physical activity, social network score, alcohol intake, tobacco use, and dietary patterns. Physical activity was categorized into mainly sedentary, 1 or fewer times per week, 2 to 4 times per week, 5 to 6 times per week, or daily. The social network score reflects how many people one regularly interacts with. It was defined as a weighted mean of 4 questions quantifying the size of an individual's social network (Item S2).[9] Alcohol intake was categorized according to World Health Organization criteria into no, moderate, or heavy intake.[21] Moderate intake was defined as 1 to 12 and 1 to 18 drinks per week for women and men, respectively, with 1 drink equaling 1.5 ounces of hard liquor or 1 glass of wine or beer. Food intake was recorded using a qualitative food frequency questionnaire,[8,14,22] measuring the number of servings one regularly consumes for 20 food groups during the past year. The questionnaire is applicable in multiple countries despite regional differences.[22] The mAHEI was used to assess adherence to dietary guidelines.[8,13,14] For each participant, frequency of consumption of 8 food groups was scored as described in Dehghan et al,[14] but additionally, multivitamins were added as in McCullough et al.[13] Each food group contributes between 0 and 10 points: higher mAHEI reflects intake of multivitamins; higher intake of vegetables, fruits, nuts, or whole grains; and lower intake of red and processed meats, fried foods, and alcohol. Estimated 24-hour urinary sodium and potassium excretion were estimated from a fasting morning urine sample.[23,24]

Study Outcome

Kidney function was measured twice during follow-up (2 and 5.5 years) and therefore the composite outcome was defined as:

(1) alive without CKD after 5.5 years, (2) alive with CKD after 5.5 years, or (3) death within follow-up. Incidence or progression of CKD was quantified as new moderate or severe albuminuria and/or decline in estimated glomerular filtration rate (eGFR). Moderate or severe albuminuria was defined as progression of urinary albumin-creatinine ratio (UACR) to >3.4 or >33.9 mg/mmol, respectively, and a ≥30% increase compared to baseline. The 30%-increase rule prevented assumed random categorical changes in 11 participants who started with a UACR slightly >3.4 or >33.9 mg/mmol. Clinically relevant eGFR decline was defined as an annual eGFR decline ≥ 5% (ie, measured as the slope over eGFR measurements for each participant), need for dialysis during follow-up, and/or eGFR ≤ 15 mL/min/1.73 m^2 at 5.5 years. UACR was measured in 1 laboratory at baseline and 5 years, and serum creatinine was measured at study sites at baseline and 5.5 years. eGFR was calculated using the CKD-EPI (CKD Epidemiology Collaboration) equation.[25]

Statistical Analysis

Continuous variables are described as median and interquartile range (IQR), categorical variables are summarized by frequency and percentage. Complete case analysis was applied because only 111 (1.6%) participants had missing values at baseline. Diabetes duration and UACR were log-transformed to avoid a disproportional influence of large values. Several multinomial logit regression models were fitted to estimate the association of each modifiable risk factor with CKD and death (single-factor models). Possibly nonlinear outcome associations of continuous factors were accounted for by using fractional polynomials with $P = 0.157$,[26] which approximately corresponds to selection by the Akaike information criterion.[27]

All single-lifestyle-factor models were adjusted for predefined confounders including (at baseline) age, sex, diabetes duration, ONTARGET randomization arm, albuminuria status, eGFR, and δ-UACR, which was defined as $\log(3.4/UACR_{baseline})$ or $\log(33.9/UACR_{baseline})$ for participants with no or moderate albuminuria.[8] The δ-UACR was modeled like this to account for the higher probability of a stage change for individuals whose baseline UACR was close to the stage-specific cutoff point and used the log scale to avoid disproportional influence of large values. No relevant correlation among confounders and between confounders and risk factors was detected. Pairwise interactions between confounders and risk factors were separately tested controlling for a false discovery rate of 5%.[28] No statistically significant and clinically relevant interaction was found.

A multivariable dietary model, including consumption of alcohol, vegetables, fruits and fruit juices, animal and plant proteins, high-carbohydrate foods, and fried foods, and urinary potassium and sodium excretion, adjusted for the same confounders, was fitted. Because modifications of lifestyle and dietary risk factors are often closely related and their effects on later outcomes are hardly separable, we refrained from estimating a comprehensive multivariable model. However, a healthy lifestyle score based on 5 modifiable risk factors was devised. Each component contributed 1 point to the healthy lifestyle score if a participant had exposure status associated with the lowest risk for CKD and mortality (mAHEI ≥ 28, BMI ≥ 23-≤30 kg/m^2, daily physical activity, social network score ≥ 25, and never smoker), 0.5 point was contributed for exposure with intermediate risk, and 0 point, for the most unfavorable exposure (mAHEI < 21, BMI < 23 or >30 kg/m^2, physical activity ≤1 time per week, social network score < 13, and current smoker). A multinomial logit model with healthy lifestyle score adjusted for the confounders was estimated.

Although multinomial logit models can be used to quantify the association of each risk factor with CKD and death, they can also serve to estimate, for each participant, the predicted probabilities of CKD and death based on the participant's confounder values and risk-factor exposures. For each participant, we estimated the probability of CKD and death if unfavorable exposure to risk factors was changed to a more favorable one. The sum of these individual probabilities is an estimate of the number of CKD cases and deaths expected under this alternative scenario. Adjusted PAFs follow as $(cases_{observed} - cases_{expected})/cases_{observed}$.[15] Unadjusted PAFs were derived from univariate models. The bootstrap percentile method (1,000 resamples) was applied to estimate 95% confidence intervals (CIs). A 2-sided $P < 0.05$ was considered statistically significant. R statistical software, version 3.0.0, was used for analysis.[29]

RESULTS

Association of Modifiable Lifestyle Factors With CKD and Death

After 5.5 years of the 6,916 individuals with type 2 diabetes and no or moderate albuminuria, 1,022 (14.8%) died and 2,165 (31.3%) had incidence or progression of CKD (Table 1; Fig S1). At baseline, median age was 66 (IQR, 61-71) years, participants had diabetes for a median of 9 (IQR, 3-16) years and a median eGFR of 72 (IQR, 58-86) mL/min/1.73 m^2, and 5,342 (77.2%) had no albuminuria (Tables 2 and Table S1).

In confounder-adjusted single-lifestyle-factor models, we detected decreased risk for CKD among individuals with a healthier diet ($P < 0.001$) and those who were physically active ($P = 0.002$), had a larger social network ($P = 0.02$), or moderately consumed alcohol (vs no alcohol, $P = 0.001$). For mortality, results were similar, but the protective effect of physical activity was more pronounced ($P < 0.001$) and current and former tobacco use increased the risk for death ($P < 0.001$). In the multivariable dietary model adjusted for the same confounders, we found lower risk for CKD in individuals with moderate alcohol

Table 1. Derivation of Study Outcome After 5.5 Years of Follow-up

Study Outcome After 5.5 y	No. (%) (n = 6,916)
Incidence or progression of CKD	2,165 (31.3)
Albuminuria	704 (32.5)
eGFR decline	1,194 (55.2)
Albuminuria & eGFR decline	267 (12.3)
Death	1,022 (14.8)
Alive without CKD	3,729 (53.9)

Note: Albuminuria, moderate or severe, was defined as progression of urinary albumin-creatinine ratio to >3.4 or >33.9 mg/mmol, respectively, and an increase of at least 30% compared to baseline. A clinically relevant eGFR decline was defined as annual decline in eGFR ≥ 5%, need for emergent or long-term dialysis during follow-up, and/or eGFR ≤ 15 mL/min/1.73 m^2 at 5.5 years. To be more precise, rather than onset and progression of CKD per se, we ascertained a decline in kidney measures after 5.5 years.

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Table 2. Characteristics of Study Population at Baseline

Characteristics at Baseline	All Individuals (n = 6,916)	No. of Vegetables Servings per Week (n = 6,887)				
		<1 (n = 177)	1-<4 (n = 725)	4-<7 (n = 1,214)	7-<14 (n = 2,393)	≥14 (n = 2,378)
Sex						
Female	2,209 (31.9)	47 (26.6)	223 (30.8)	357 (29.4)	767 (32.1)	807 (33.9)
Male	4,707 (68.1)	130 (73.4)	502 (69.2)	857 (70.6)	1,626 (67.9)	1,571 (66.1)
Age, y	66 [61-71]	67 [61-72]	66 [62-71]	66 [60-71]	66 [61-71]	65 [60.2-71]
Duration of diabetes, y	9 [3-16]	9 [3-18]	10 [4-16]	9 [3-15]	9 [3-16]	8 [3-16]
UACR, mg/mmol	6.6 [2.9-25.0]	6.5 [2.4-25.9]	7.4 [3-29.3]	7.3 [2.8-27.1]	6.9 [2.9-25.6]	6.0 [2.8-22.8]
eGFR, mL/min/1.73 m^2	71.5 [58.1-85.9]	73 [58.5-86.8]	71.1 [57.5-84.1]	71.9 [58.6-84.5]	71.5 [58-87.3]	71.3 [58.3-85.8]
Albuminuria						
No	5,342 (77.2)	139 (78.5)	547 (75.4)	926 (76.3)	1,840 (76.9)	1,868 (78.6)
Moderate	1,574 (22.8)	38 (21.5)	178 (24.6)	288 (23.7)	553 (23.1)	510 (21.4)
eGFR category						
≥60	4,663 (67.4)	125 (70.6)	495 (68.3)	809 (66.6)	1,615 (67.5)	1,603 (67.4)
30-59.9	2,159 (31.2)	49 (27.7)	219 (30.2)	393 (32.4)	737 (30.8)	748 (31.5)
15-29.9	91 (1.3)	2 (1.1)	10 (1.4)	12 (1.0)	40 (1.7)	27 (1.1)
<15	3 (0.1)	1 (0.6)	1 (0.1)	0 (0.0)	1 (0.0)	0 (0.0)
Kidney function & albuminuria						
eGFR ≥ 60 & no	920 (13.3)	22 (12.4)	113 (15.6)	175 (14.4)	305 (12.8)	301 (12.7)
eGFR ≥ 60 & moderate	3,743 (54.1)	103 (58.2)	382 (52.7)	634 (52.2)	1,310 (54.7)	1,302 (54.7)
eGFR 30-59.9 & no	611 (8.9)	15 (8.4)	55 (8.0)	110 (9.1)	224 (9.4)	201 (8.5)
eGFR 30-59.9 & moderate	1,548 (22.4)	34 (19.2)	52 (7.2)	283 (23.4)	513 (21.4)	547 (23.0)
eGFR 15-29.9 & no	42 (0.6)	1 (0.6)	7 (1.0)	3 (0.2)	23 (1.0)	8 (0.3)
eGFR 15-29.9 & moderate	49 (0.7)	1 (0.6)	3 (0.4)	9 (0.7)	17 (0.7)	19 (0.8)
eGFR < 15 & no	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
eGFR < 15 & moderate	2 (0.0)	1 (0.6)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
ONTARGET randomization						
Ramipril	2,251 (32.6)	67 (37.9)	236 (32.6)	384 (31.6)	768 (32.1)	786 (33.1)
Telmisartan	2,304 (33.3)	62 (35.0)	240 (33.1)	401 (33.0)	778 (32.5)	813 (34.2)
Combination	2,361 (34.1)	48 (27.1)	249 (34.3)	429 (35.3)	847 (35.4)	779 (32.8)
Ethnicity						
White	4,699 (67.9)	124 (70.1)	487 (67.2)	902 (74.3)	1,758 (73.5)	1,403 (59)
Asian	1,173 (17.0)	8 (4.5)	86 (11.9)	135 (11.1)	317 (13.2)	627 (26.4)
Native Latin	650 (9.4)	37 (20.9)	112 (15.4)	113 (9.3)	202 (8.4)	183 (7.7)
Others	394 (5.7)	8 (4.5)	40 (5.5)	64 (5.3)	116 (4.8)	165 (6.9)
Region						
Europe	3,088 (44.6)	90 (50.8)	357 (49.2)	686 (56.5)	1,175 (49.1)	769 (32.3)
North & South America	2,247 (32.5)	76 (42.9)	270 (37.2)	356 (29.3)	773 (32.3)	756 (31.8)
Asia & Australia	1,341 (19.4)	9 (5.1)	83 (11.4)	132 (10.9)	365 (15.3)	752 (31.6)
Rest of world	240 (3.5)	2 (1.1)	15 (2.1)	40 (3.3)	80 (3.3)	101 (4.2)

Note: Values for categorical variables are given as frequency (percentage); for continuous variables, as median [interquartile range]. eGFRs expressed in mL/min/1.73 m^2.

Abbreviations: eGFR, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration formula[25]; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; UACR, urinary albumin-creatinine ratio.

intake (vs no alcohol, $P = 0.003$), higher urinary potassium excretion ($P = 0.001$), or higher intake of vegetables ($P = 0.02$) and animal ($P = 0.003$) and plant proteins ($P = 0.02$). Rates of CKD and death for lifestyle factors are given in Table 3, highlighting the differences in risk.

We summarized adherence to 5 healthy behaviors in a 5-point healthy lifestyle score (Table 4). A very good healthy lifestyle score > 3.5 was observed in 1,589 (23.2%) participants, whereas 819 (11.9%) had a healthy lifestyle score ≤ 1. Individuals with higher scores had significantly reduced risk for CKD and death.

Evaluation of Possible Lifestyle Intervention Strategies

Based on these data, we calculated PAFs corresponding to various scenarios of unfavorable lifestyle exposures. If there is a causal relationship between

Table 3. Distribution of Modifiable Lifestyle and Dietary Risk Factors of Study Population at Baseline

Characteristic	No. (%)	Baseline No. (%), by Outcome	
		CKD	Death
Modifiable lifestyle characteristics			
BMI (n = 6,883)			
15-<23 kg/m^2[a]	493 (7.2)	156 (31.6)	91 (18.5)
23-<25 kg/m^2	832 (12.1)	229 (27.5)	140 (16.8)
25-<30 kg/m^2	2,873 (41.7)	889 (30.9)	428 (14.9)
30-<35 kg/m^2	1,827 (26.5)	584 (32.0)	235 (12.9)
35-<50 kg/m^2	858 (12.5)	298 (34.7)	122 (14.2)
Physical activity (n = 6,913)			
Mainly sedentary	1,659 (24.0)	569 (34.3)	322 (19.4)
≤1×/wk	806 (11.7)	250 (31.0)	121 (15.0)
2-4×/wk	1,583 (22.9)	498 (31.5)	208 (13.1)
5-6×/wk	474 (6.9)	146 (30.8)	65 (13.7)
Daily	2,391 (34.6)	701 (29.3)	305 (12.8)
Social network score (n = 6,898)			
0%-<8%	1,244 (18.0)	412 (33.1)	237 (19.1)
8%-<13%	1,219 (17.7)	382 (31.3)	178 (14.6)
13%-<25%	2,144 (31.1)	666 (31.1)	310 (14.5)
25%-100%	2,291 (33.2)	703 (30.7)	293 (12.8)
Alcohol intake (n = 6,914)[b]			
None	4,678 (67.7)	1,541 (32.9)	718 (15.4)
Moderate	2,058 (29.8)	570 (27.7)	282 (13.7)
High	178 (2.6)	53 (29.8)	22 (12.4)
Tobacco use (n = 6,907)			
Never	2,759 (39.9)	902 (32.7)	359 (13.0)
Former	755 (10.9)	213 (28.2)	144 (19.1)
Current	3,393 (49.1)	1,047 (30.9)	518 (15.3)
Modifiable dietary risk factors			
mAHEI (n = 6,916)			
9-<21	2,271 (32.8)	766 (33.7)	423 (18.6)
21-<28	2,303 (33.3)	736 (32.0)	327 (14.2)
28-67	2,342 (33.9)	663 (28.3)	272 (11.6)
Est 24-h urinary potassium (n = 6,903)			
0.8-<1.5 g	421 (6.1)	149 (35.4)	58 (13.8)
1.5-<1.9 g	1,758 (25.5)	546 (31.1)	268 (15.2)
1.9-<2.4 g	2,528 (36.6)	802 (31.7)	388 (15.4)
2.4-5.0 g	2,196 (31.8)	663 (30.2)	308 (14.0)
Est 24-h urinary sodium (n = 6,901)			
0.6-<3.0 g	734 (10.6)	248 (33.8)	133 (18.1)
3.0-<4.5 g	2,042 (29.6)	610 (29.9)	323 (15.8)
4.5-<6.0 g	2,457 (35.6)	772 (31.4)	312 (12.7)
6.0-10.0 g	1,668 (24.2)	529 (31.7)	253 (15.2)
Fried foods: trans fat (n = 6,901)			
No	3,657 (53.0)	1,149 (31.4)	536 (14.7)
Yes	3,244 (47.0)	1,009 (31.1)	484 (14.9)
High-carbohydrate foods (n = 6,889)			
0-<1 servings/wk	699 (10.1)	210 (30.0)	88 (12.6)
1-<4 servings/wk	1,252 (18.2)	397 (31.7)	177 (14.1)
4-<7 servings/wk	851 (12.4)	282 (33.1)	135 (15.9)
7-<14 servings/wk	1,652 (24.0)	493 (29.8)	247 (15.0)
14-49 servings/wk	2,435 (35.3)	773 (31.8)	371 (15.2)
Fruit and fruit juices (n = 6,894)			
0-<1 servings/wk	295 (4.3)	99 (33.6)	52 (17.6)
1-<4 servings/wk	1,047 (15.2)	351 (33.5)	184 (17.6)
4-<7 servings/wk	1,603 (23.3)	492 (30.7)	228 (14.2)
7-<14 servings/wk	2,436 (35.2)	771 (31.7)	347 (14.2)
14-28 servings/wk	1,513 (22.0)	443 (29.38)	208 (13.8)
Vegetables (n = 6,887)			
0-<1 servings/wk	177 (2.6)	66 (37.3)	33 (18.6)
1-<4 servings/wk	725 (10.5)	227 (31.3)	154 (21.2)
4-<7 servings/wk	1,214 (17.6)	393 (32.4)	180 (14.8)
7-<14 servings/wk	2,393 (34.8)	769 (32.1)	345 (14.4)
14-35 servings/wk	2,378 (34.53)	698 (29.4)	307 (12.9)
Leafy green vegetables (n = 6,894)			
0-<1 servings/wk	853 (12.4)	295 (34.6)	161 (18.9)
1-<4 servings/wk	2,864 (41.5)	893 (31.2)	429 (15.0)
4-<7 servings/wk	218 (3.2)	75 (34.4)	25 (11.5)
7-<14 servings/wk	1,947 (28.2)	609 (31.3)	272 (14.0)
14 servings/wk	1,012 (14.7)	283 (28.0)	132 (13.0)
Animal protein (n = 6,894)			
0.00-<0.40 g/kg/d	2,669 (38.7)	890 (33.4)	403 (15.1)
0.40-<0.60 g/kg/d	2,033 (29.5)	622 (30.6)	303 (14.9)
0.60-2.45 g/kg/d	2,192 (31.8)	643 (29.3)	314 (14.3)
Plant protein (n = 6,889)			
0.00-<0.07 g/kg/d	2,352 (34.1)	748 (31.8)	362 (15.4)
0.07-<0.15 g/kg/d	2,565 (37.2)	806 (31.4)	395 (15.4)
0.15-0.65 g/kg/d	1,972 (28.6)	601 (30.5)	261 (13.2)
Total protein (n = 6,887)			
0.00-<0.47 g/kg/d	2,270 (33.0)	772 (34.0)	341 (15.0)
0.47-<0.66 g/kg/d	1,887 (27.4)	594 (31.5)	291 (15.4)
0.66-<0.85 g/kg/d	1,163 (16.9)	344 (29.6)	154 (13.2)
0.85-2.65 g/kg/d	1,567 (22.8)	444 (28.3)	232 (14.8)

Note: For descriptive purposes only, continuous risk factors were categorized. The number of available observations and frequencies and percentages of cases of incidence or progression of CKD and deaths in each category are given.

Abbreviations: BMI, body mass index; CKD, (incidence or progression of) chronic kidney disease; Est, estimated; mAHEI, modified Alternate Healthy Eating Index.

[a]Of the 493 (7.2%) individuals with such a BMI, 156 (31.6%) had CKD after 5.5 years and 91 (18.5%) died within these 5.5 years.

[b]Alcohol was categorized by sex-specific World Health Organization guidelines. Moderate intake was defined as 1 to 12 and 1 to 18 drinks per week for women and men, respectively.

lifestyle factors and CKD and death, one can use these PAFs to evaluate the impact of various possible lifestyle interventions on the relative reduction in CKD

Table 4. Healthy Lifestyle Score and Incidence or Progression of CKD and Death

HLS Score

HLS Points[a]	Distribution, %	$\%_{CKD}$[b]	OR_{CKD} (95% CI)	$\%_{Death}$[c]	OR_{Death} (95% CI)
0-1	11.9	35.0	1.00 (reference)[d]	19.0	1.00 (reference)[d]
1.5	12.6	34.2	0.88 (0.83 to 0.92)	18.2	0.76 (0.71 to 0.82)
2	16.8	31.2	0.82 (0.76 to 0.89)	15.3	0.67 (0.60 to 0.75)
2.5	18.9	29.6	0.76 (0.69 to 0.85)	15.1	0.59 (0.51 to 0.68)
3	16.6	32.0	0.72 (0.63 to 0.82)	14.8	0.51 (0.43 to 0.61)
>3.5	23.2	29.1	0.58 (0.47 to 0.72)[e]	9.8	0.34 (0.26 to 0.46)[e]

Outcomes

		CKD		Death	
HLS Alternative Level	% of People Who Must Be Shifted	PAF, %	Excess Attributable Cases, in 1,000	PAF, %	Excess Attributable Cases, in 1,000
<1 → 1	4	0.09 (−0.01 to 0.20)	5	0.59 (0.38 to 0.84)	15
<1.5 → 1.5	12	0.32 (0.00 to 0.66)	18	1.77 (1.16 to 2.47)	46
<2 → 2	25	0.85 (0.11 to 1.62)	47	4.06 (2.72 to 5.56)	105
<2.5 → 2.5	41	1.81 (0.41 to 3.28)	102	7.68 (5.24 to 10.33)	200
<3 → 3	60	3.30 (0.93 to 5.76)	186	12.64 (8.78 to 16.74)	328
<3.5 → 3.5	77	5.31 (1.66 to 8.93)	299	18.55 (13.13 to 24.16)	481
<5 → 5[f]	99	13.29 (5.54 to 20.86)	747	37.46 (27.77 to 46.67)	973
<X → X+1[g]	99	4.87 (1.78 to 7.91)	274	15.58 (11.21 to 20.02)	405
<X → X+2	99	9.29 (3.71 to 14.82)	522	27.67 (20.24 to 34.96)	718

Note: The HLS summarizes adherence to 5 healthy behaviors and ranges from 0 to 5 (optimal level). A multinomial logit model with the HLS adjusted with (at baseline) age, sex, duration of diabetes, ONTARGET randomization arm, albuminuria status, eGFR, and δ-UACR, which was defined as $\log(3.4/UACR_{baseline})$ or $\log(33.9/UACR_{baseline})$ for patients with no or moderate albuminuria, was estimated (n = 6,854). PAFs for CKD (after 5.5 years) and 5.5-year mortality, which quantify the proportional reductions of incidence or progression of CKD and death that would occur if the exposure to a modifiable risk factor had been shifted to an alternative (ie, optimal) level, are given with 95% CIs for different scenarios; for example, "<1.5 → 1.5" means that individuals with an HLS < 1.5 improve their HLS to 1.5, whereas individuals with an HLS ≥ 1.5 do not change their HLS. "Excess attributable cases, in 1,000" were extrapolated from the ONTARGET cohort to the approximately 17.8 million individuals older than 44 years with diagnosed diabetes in the United States; assuming that this population is comparable to the ONTARGET population. Based on our results, approximately 5.6 million cases of CKD (after 5.5 years) and 2.6 million deaths (within 5.5 years) can be expected in this population. Unadjusted PAFs and excess attributable cases for the population of middle-aged individuals with diabetes in the European Union are given in Table S2.

Abbreviations: BMI, body mass index; CI, confidence interval; CKD, (incidence of progression of) chronic kidney disease; eGFR, estimated glomerular filtration rate; HLS, healthy lifestyle score; mAHEI, modified Alternate Healthy Eating Index; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; OR, odds ratio; PAF, population-attributable fraction; UACR, urinary albumin-creatinine ratio.

[a]One point was awarded for being in the category with lowest risk (mAHEI ≥ 28, BMI of 23-≤30 kg/m^2, daily physical activity, social network score ≥ 25, never smoker), 0.5 point for the category with intermediate risk, and 0 point for the category with the highest risk (mAHEI < 21, BMI < 23 or >30 kg/m^2, physical activity ≤ 1×/wk, social network score < 13, current smoker).

[b]Percentage of cases of incidence or progression of CKD in each category of the score.

[c]Percentage of deaths in each category of the score.

[d]Reference category is HLS of 0.5.

[e]ORs are given for HLS of 4.5.

[f]A very unrealistic scenario in which everyone is shifted to the category with the lowest risk in all 5 areas of lifestyle.

[g]A more realistic scenario in which everyone increases his or her score by 1, ie, 1 lifestyle behavior is improved to the optimal level. (Individuals with an optimal score of 5 do not change and individuals with a score of 4.5 increase by only 0.5).

cases and deaths, assuming full adherence to such interventions (Table 5). If individuals with a suboptimal diet (eg, mAHEI < 28) reached an mAHEI of 28, PAFs are 2.4% (95% CI, 0.3%-4.6%) for CKD after 5.5 years and 13.8% (95% CI, 9.8%-17.4%) for death within 5.5 years. If individuals with BMI < 23 or >30 kg/m^2 achieved a BMI of 23 or 30 kg/m^2, PAFs for CKD and death are 1.5% (95% CI, −0.1% to 3.0%) and 1.7% (95% CI, −0.5% to 4.3%). If everyone were physically active every day, PAFs are 5.1% (95% CI, 0.5%-9.6%) for CKD and 12.3% (95% CI, 4.9%-19.1%) for death. A social network of 25 or fewer people would reduce the estimated fractions by 1.2% (95% CI, −0.9% to 3.4%) for CKD and 6.3% (95% CI, 3.0% to 9.7) for death.

Among all dietary modifications, the largest impact on CKD and death results from increasing vegetable intake, especially leafy green vegetables. If everyone

Table 5. PAFs of Modifiable Lifestyle and Dietary Risk Factors for Incidence or Progression of CKD and Death

Modifiable Risk Factors and Alternative Levels	% of People Shifted	CKD		Death	
		PAF, %	Excess Attributable Cases, in 1,000	PAF, %	Excess Attributable Cases, in 1,000
mAHEI					
<28 → 28	66	2.41[a]	135	13.77[a]	358
<21 → 21	33	0.52	29	3.90[a]	101
BMI[b]					
<23 → 23 & >30 → 30 kg/m^2	46	1.45	82	1.67	44
>30 → 30 kg/m^2	39	1.52[a]	85	1.15	30
Physical activity[c]					
0-6 → 7×/wk	65	5.08[a]	286	12.29[a]	319
≤1 → 2-4×/wk & 2-6 → 7×/wk	65	2.66	149	10.23[a]	266
≤1-6 → 7×/wk[d]	41	2.40	135	3.70	96
Social network score					
<25 → 25	67	1.18	66	6.28[a]	163
<13 → 13	36	0.46	26	2.89[a]	75
Alcohol intake[e]					
None, high → moderate	70	8.77[a]	493	5.03	131
High → moderate	3	0.17	9	−0.15	−4
Tobacco use[f]					
Current → former[g]	49	−0.98	−55	4.76[a]	124
Former, current → never	60	−1.66	−93	13.70[a]	356
Vegetables					
<21 → 21 servings/wk	83	2.24	126	12.61[a]	327
<14 → 14 servings/wk	60	1.59	89	9.04[a]	235
<7 → 7 servings/wk	26	0.80	45	4.19[a]	109
<4 → 4 servings/wk	13	0.51	29	1.89[a]	49
X → X+2 servings/wk	100	0.89	50	4.10[a]	107
Leafy green vegetables					
<7 → 7 servings/wk	57	2.38[a]	134	6.90[a]	179
<4 → 4 servings/wk	54	1.53	86	4.70[a]	122
<2 → 2 servings/wk	34	0.81	46	2.71[a]	70
X → X+2 servings/wk	100	1.72[a]	96	5.06[a]	131
Fruits and fruit juices					
<21 → 21 servings/wk	84	3.50	197	11.27[a]	292
<14 → 14 servings/wk	58	2.39	134	7.79[a]	202
<7 → 7 servings/wk	24	1.03	58	3.34[a]	86
<4 → 4 servings/wk	19	0.55	31	1.60[a]	41
X → X+2 servings/wk	100	1.02	57	3.15[a]	82
Total protein[h]					
<0.85 → 0.85 g/kg/d	77	4.41[a]	248	3.22	84
<0.7 → 0.7 g/kg/d	65	2.64[a]	149	1.91	50
<0.66 → 0.66 g/kg/d	60	2.23[a]	126	1.61	41
Animal protein					
<0.6 → 0.6 g/kg/d	68	2.70[a]	151	1.71	44
<0.4 → 0.4 g/kg/d	39	0.85[a]	47	0.53	14
Plant protein					
<0.15 → 0.15 g/kg/d	71	1.94	109	3.08	80
<0.07 → 0.07 g/kg/d	34	0.41	23	0.66	17
High-carbohydrate foods					
>4 → 4 servings/wk	72	0.25	14	1.31[a]	34
>7 → 7 servings/wk	59	0.11	6	0.62[a]	16
>14 → 14 servings/wk	35	0.03	1	0.15[a]	4

(Continued)

Table 5 (Cont'd). PAFs of Modifiable Lifestyle and Dietary Risk Factors for Incidence or Progression of CKD and Death

Modifiable Risk Factors and Alternative Levels	% of People Shifted	CKD		Death	
		PAF, %	Excess Attributable Cases, in 1,000	PAF, %	Excess Attributable Cases, in 1,000
Fried foods					
Yes → no	47	0.51	29	2.14	56
Est 24-h urinary potassium					
<2.4 → 2.4 g	68	3.40[a]	191	0.80	20
<1.9 → 1.9 g	32	0.82[a]	46	0.18	4
Est 24-h urinary sodium[i]					
>1.5 → 1.5 g	99	−6.12	−344	−40.99	−1,064
<3 → 3 & >6 → 6 g	35	−0.06	−4	3.55[a]	92
<3 → 3 g	11	0.12	6	1.55[a]	40
>6 → 6 g	24	−0.17	−10	1.93[a]	50

Note: For each lifestyle and dietary risk factor, a separate (adjusted) multinomial logit model was estimated and the impact on population health, quantified by PAFs, was computed for several scenarios. The model was adjusted with (at baseline) age, sex, duration of diabetes, ONTARGET randomization arms, albuminuria status, eGFR, and d-UACR, which was defined as $\log(3.4/UACR_{baseline})$ or $\log(33.9/UACR_{baseline})$ for patients with no or moderate albuminuria. "Excess attributable cases, in 1,000" were extrapolated from the ONTARGET cohort to the approximately 17.8 million individuals older than 44 years with diagnosed diabetes in the United States. For a description of the interpretation of the PAF and excess attributable cases, refer to Table 4. Unadjusted PAFs, 95% confidence intervals for adjusted PAFs, and excess attributable cases for the population of middle-aged individuals with diabetes in the European Union are given in Table S3.

Abbreviations: BMI, body mass index; CKD, (incidence or progression of) chronic kidney disease; Est, estimated; mAHEI, modified Alternate Healthy Eating Index; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; PAF, population-attributable fraction.

[a]PAFs significant at $\alpha = 0.05$.

[b]World Health Organization recommendations for a healthy BMI range from 18.5 to 25.0 kg/m^2 for adults.[46] However, these recommendations might be too restrictive for the elderly because it has been shown that for people older than 64 years, the risk for mortality increases with BMI < 23 or > 30 kg/m^2.[47]

[c]Physical activity is categorized into being mainly sedentary and being physical active ≤1×/wk, 2-4×/wk, 5-6×/wk, and daily (7×/wk).

[d]Assuming individuals who are mainly sedentary cannot change their physical activity due to health issues.

[e]Alcohol intake was categorized according to sex-specific World Health Organization guidelines. Moderate intake defined as 1 to 12 and 1 to 18 drinks per week for women and men, respectively.

[f]Tobacco use is categorized into never, former, and current smoker.

[g]The negative PAF for the competing risk for CKD is likely due to life years gained after cessation of smoking.

[h]For healthy adults, the estimated average protein requirement is 0.66 g/kg/d and the recommended dietary allowance is 0.80.[48] Campbell et al[48] suggested that protein requirements for older people are not statistically different and estimated an adequate protein allowance to be 0.85 g/kg/d.

[i]Dietary guidelines for Americans recommend a maximum sodium intake of 1.5 g/d for people older than 50 years.[49] However, O'Donnell et al showed that an estimated sodium intake between 3 and 6 g/d was associated with a lower risk for death and cardiovascular events.[50-53]

ate 2 additional servings of leafy green vegetables per week, PAFs are 1.7% (95% CI, 0.0%-3.6%) for CKD and 5.1% (95% CI, 2.3%-7.9%) for death. Another strategy could be to motivate individuals to consume at least 3 servings of vegetables per day, which would reduce the estimated fractions of CKD and death by 2.2% (95% CI, −0.8% to 5.4%) and 12.6% (95% CI, 8.3% to 17.1%). For CKD, a similar value could be achieved by increasing the number of servings of fruits and fruit juices to at least 2 per day (PAF, 2.4%; 95% CI, −0.2% to 5.0%). Low total protein intake (<0.85 g/kg/d) yields PAFs of 4.4% (95% CI, 1.7% to 7.2%) for CKD and 3.2% (95% CI, −1.2% to 7.3%) for death. Increasing minimum potassium excretion to 2.4 g corresponds to PAF reductions of 3.4% (95% CI, 1.2% to 5.6%) for CKD and 0.80% (95% CI, −2.7% to 4.1%) for death.

Whereas PAFs derived from single lifestyle factor models estimate the potential reduction in CKD or death of 1 lifestyle intervention, PAFs from a multivariable model offer additional information of the possible reduction of simultaneous lifestyle interventions. The multivariable dietary model suggests that although a reduction in alcohol intake would have the largest impact on CKD, increasing vegetable intake may have the largest impact on mortality (Table 6). Changing all dietary factors to the assumed optimal levels yields PAFs of 20.5% (95% CI, 12.3%-27.4%) for CKD and 29.8% (95% CI, 19.5%-39.2%) for death.

Table 6. Multivariable Dietary Model and PAF of Dietary Risk Factors for Incidence or Progression of CKD and Death

			CKD		Death	
Modifiable Dietary Factors	Alternative Levels	% of People Shifted	PAF, %	Excess Attributable Cases, in 1,000	PAF, %	Excess Attributable Cases, in 1,000
Modify each risk factor separately						
Alcohol intake[a]	None, high → moderate	70	8.09	454	4.89	127
Vegetables	<21 → 21 servings/wk	83	1.02	57	12.14	315
Fruits & fruit juices	<14 → 14 servings/wk	58	1.22	68	4.87	126
Animal protein	<0.6 → 0.6 g/kg/d	68	2.70	152	0.17	4
Plant protein	<0.15 → 0.15 g/kg/d	71	1.93	108	2.56	67
High-carbohydrate foods	>7 → 7 servings/wk	59	0.46	26	2.38	62
Fried foods	Yes → no	47	0.95	53	0.98	25
Est 24-h urinary potassium	<2.4 → 2.4 g	68	3.71	209	0.26	7
Est 24-h urinary sodium	<3 → 3 & >6 → 6 g	35	0.10	6	3.54	92
Modify all risk factors simultaneously		100	20.48	1,147	29.81	775

Note: Adjusted PAFs of incidence or progression of CKD after 5.5 years and 5.5-year mortality of dietary food groups from the multivariable model adjusted with (at baseline) age, sex, duration of diabetes, ONTARGET randomization arms, albuminuria status, eGFR, and d-UACR, which was defined as $\log(3.4/UACR_{baseline})$ or $\log(33.9/UACR_{baseline})$ for patients with no or moderate albuminuria. "Excess attributable cases, in 1,000" were extrapolated from the ONTARGET cohort to the approximately 17.8 million individuals older than 44 years with diagnosed diabetes in the United States. For a description of the interpretation of the PAF and excess attributable cases, refer to Table 4. PAFs are given for 2 scenarios; either only 1 food group is changed according to the alternative level (and all other food groups remain constant) or all food groups are changed to their respective alternative levels simultaneously. Unadjusted PAFs, 95% confidence intervals, and excess attributable cases for the population of middle-aged individuals with diabetes in the European Union for adjusted PAFs are given in Table S4.

Abbreviations: CKD, (incidence or progression of) chronic kidney disease; eGFR, estimated glomerular filtration rate; Est, estimated; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; PAF, population-attributable fraction; UACR, urinary albumin-creatinine ratio.

[a]Alcohol intake is categorized according to sex-specific World Health Organization guidelines. Moderate intake was defined as 1 to 12 and 1 to 18 drinks per week for women and men, respectively.

If individuals improved their healthy lifestyle scores to ≥3.5, reductions in estimated fractions for CKD and death would be 5.3% (95% CI, 1.7%-8.9%) and 18.6% (95% CI, 13.1%-24.2%; Table 4). Another strategy could be that everyone with a suboptimal healthy lifestyle score improves their score by 1 point (ie, improving 1 suboptimal behavior to the optimal range), which gives PAFs of 4.9% (95% CI, 1.8%-7.9%) for CKD and 15.6% (95% CI, 11.2%-20.0%) for death. Improving the healthy lifestyle score by 2 points corresponds to PAFs of 9.3% (95% CI, 3.7%-14.8%) for CKD and 27.7% (95% CI, 20.2%-35.0%) for death.

DISCUSSION

This large observational cohort study suggests that exposure to unfavorable levels in diet, weight, physical activity, social network, and tobacco use is attributable for up to 13% of cases of CKD incidence or progression (after 5.5 years) and 38% of deaths (within 5.5 years) among individuals 55 years or older with diabetes. In the approximately 17.8 million middle-aged individuals with diagnosed diabetes in the United States, this would correspond to a potential reduction of approximately 750,000 cases of CKD (after 5.5 years). It is not realistic that optimal exposure for these aspects of lifestyle can be attained by all individuals. However, our results concerning healthy lifestyle score, composed of 5 dimensions of lifestyle behavior, suggest that if everyone improved just 1 behavior, CKD could be reduced by 5%, and 5.5-year mortality, by 16%. A very similar definition of healthy lifestyle in the European Prospective Investigation into Cancer and Nutrition (EPIC) study showed that individuals with a generally healthy lifestyle had a 78% lower overall risk for developing a chronic disease.[30]

A healthy diet has been shown to support the prevention and management of diabetes.[31] Adherence to a high-quality diet as measured by the mAHEI was strongly associated with reduced risk for diabetes.[32] Our results suggest that such a diet can also reduce CKD. The American Diabetes Association does not recommend that people with diabetes and kidney disease decrease their protein intake.[33,34] Our analysis shows that a minimum intake of 0.85 g/kg/d of protein could reduce CKD by 4% and 5.5-year mortality by 3%. However, 77% of the ONTARGET population would have to increase protein consumption to reach this goal. A secondary analysis of the Look AHEAD (Action for Health in Diabetes) trial showed that an intensive lifestyle intervention resulting in weight loss should be considered in reducing CKD in individuals with diabetes.[35] Similarly, our results show that if everyone had a BMI of 23 to 30 kg/m^2, ∼2% of both CKD cases and 5.5-year mortality could be avoided.

Daily physical activity could reduce CKD and 5.5-year mortality by 5% and 12%, respectively, underscoring the importance of public health efforts to increase physical activity. Even increasing one's social network, that is, the number of people one regularly interacts with, could have a noticeable impact on population health. In individuals with diabetes, a larger social network also supports personal self-management and physical and mental well-being.[36] A meta-analysis for cancer mortality showed that social support might prolong life and that its effects are clinically meaningful.[37] The social network may affect health behavior, and individuals with a larger social network may have more reliable access to the health care system. A biological explanation is that low social support is associated with shorter telomere length in older individuals.[38] Another meta-analysis for the general population discussed that the effect of an adequate social network on survival is comparable to cessation of tobacco use.[39]

Although PAF is a very useful epidemiologic measure, it should be interpreted with care: the concept of PAF presupposes a causal relationship between risk factors and an outcome, which cannot be verified with observational data. It is derived for a specific population and should only be applied to comparable populations with similar exposure frequencies: ONTARGET comprised middle-aged individuals with diabetes and high cardiovascular risk. All participants received angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and most were treated according to guidelines with preventive cardiovascular drugs and were at target blood pressures. Depending on region-specific differences, for example, smoking habits or vegetable intake, the impact on public health may be different. The PAF does not incorporate reversibility of exposures and risk latency (eg, smokers can never reach the low-risk category never smokers). Hence, a PAF resulting from shifting current smokers to former smokers (without changing the status of nonsmokers) will quantify the maximum attainable short-term effects of an antismoking campaign. From a public health perspective, the long-term effects of a preventive strategy, trying to minimize the incidence of smoking in younger people, will be considered by a PAF in which all current and former smokers are shifted to the nonsmoker category. However, risk latency may sometimes be overestimated because lifestyle modifications can have surprising short-term effects. For example, in Italy shortly after the ban of smoking in all indoor public places, a noticeable reduction in hospital admissions for acute myocardial infarction was detected.[40] Ornish et al[41,42] showed that comprehensive lifestyle changes had a positive effect on telomerase activity and telomere length after only 3 months. In multicausal diseases such as CKD, different interventions might be applied for disease prevention, leading to similar reductions in incidence. The specific choice of interventions may be based on associated costs or individual preferences. The PAF should be regarded as the maximum attainable impact on disease load because lifestyle interventions will not permanently shift all individuals to the category with the lowest risk. However, knowledge of potential reversible risks and their impact can help prioritize intervention programs and guide patient education. Dietary interventions have an additional trade-off (ie, increased vegetable intake while maintaining caloric neutrality is linked with a decline in another food group, which may affect PAF).

Measurement errors in self-reported variables are inevitable, as in any observational study. However, misclassifications are likely to be independent of the outcome and should not induce systematic bias. We assessed decline in kidney measures rather than incidence and progression of CKD. Lifestyle factors and laboratory values were measured only once at baseline. However, self-initiated lifestyle changes are rare. Strengths of this study include a large number of CKD cases observed in more than 30,000 patient-years. We controlled for potential confounders and the competing risk for mortality. The food frequency questionnaire and mAHEI have been used successfully.[13,14,22] Recommendations with regard to food groups are epidemiologically more meaningful than recommending specific nutrients.[43] Because intervention studies of the effects of lifestyle and/or dietary modifications would require a large sample size and considerable economic resources and would most likely not include kidney function as a primary outcome, a carefully conducted observational study may at least provide some guidelines on the impact of lifestyle modifications.

One may argue that the PAFs of these modifiable risk factors are often not very large. However, all these lifestyle and dietary factors are also known risk factors for other conditions such as cardiovascular disease, affect diabetes management, and have a wide range of well-known health benefits.[44,45] The PAF quantifies potential health gains through disease prevention by reduction of known risks. It is a useful tool for health communication and may raise public awareness and awareness of individuals with diabetes on improved health expectancy and decreased risk for CKD and mortality by adopting a healthier lifestyle. Lifestyle changes are not easy and not always achievable, but they have been shown to be affordable effective prevention strategies. In the 17.8 million middle-aged individuals with diagnosed diabetes in the United States, improving just 1 of 5 lifestyle behaviors to the optimal range could reduce CKD after 5.5 years by 274,000 and the number of deaths within 5.5 years by 405,000.

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Contributions: Research idea and study design: DD, KKT, GH, JFEM, SY, RO; data acquisition: KKT, SY; statistical analysis: MK, PG, DD; data analysis/interpretation: GH, RO, DD, MD, CMC. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. DD and RO take responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Peer Review: Evaluated by 2 external peer reviewers, a Statistical Editor, a Co-Editor, and the Editor-in-Chief.

SUPPLEMENTARY MATERIAL

Table S1: Comparison of characteristics at baseline for participants included in vs excluded from study.

Table S2: Healthy lifestyle score and PAF for incidence or progression of CKD and death.

Table S3: PAFs of modifiable lifestyle and dietary risk factors for incidence or progression CKD and death.

Table S4: Multivariable dietary model and PAF of dietary risk factors for incidence or progression of CKD and death.

Figure S1: Flow chart of number of participants for study outcome after 5.5 y of follow-up.

Item S1: The ONTARGET Investigators.

Item S2: Assessment of modifiable lifestyle factors.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2015.12.019) is available at www.ajkd.org

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