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Original article

Compliance with the DASH diet and risk of all-cause and cardiovascular mortality in patients with myocardial infarction

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SUMMARY

Background & aims: The Dietary Approaches to Stop Hypertension (DASH) diet has been shown to effectively reduce blood pressure and body weight, but its effectiveness for reducing (cardiovascular) mortality rates has never been assessed in a clinical trial. Causal effects of dietary interventions are difficult to measure, due to practical limitations of randomized controlled diet trials. Target trial emulation can be used to improve causal inference in observational data. The aim of this study was to emulate a target trial assessing the relationship between compliance with the DASH diet and cardiovascular and all-cause mortality risk in patients with established CVD.

Methods: Using data from the Alpha Omega Cohort, we emulated a DASH diet trial in patients with a history of myocardial infarction (MI). Inverse probability of treatment weighting (IPTW) was used to balance confounders over DASH-compliant and non-DASH-compliant participants. Hazard ratios (HRs) were estimated with IPT-weighted Cox models.

Results: Of 4365 patients (79% male, median age 69 years, >80% treated with lipid- and blood pressure-lowering medication), 598 were classified as DASH-compliant (compliance score $\geq$5 out of 9). During a median follow-up of 12.4 years, 2035 deaths occurred of which 903 (44%) were of cardiovascular origin. DASH compliance was not associated with all-cause mortality (HR 0.92, 95%CI 0.0.80–1.06) and cardiovascular mortality (HR 0.90, 95%CI 0.72–1.11).

Conclusions: In an emulated target trial on the DASH diet in the Alpha Omega cohort no relation was found between DASH compliance and risk of all-cause and cardiovascular mortality in patients with a history of MI. The DASH diet's effects may have been modified in this population by concomitant use of blood pressure-lowering medications.

1. Introduction

Cardiovascular disease (CVD) is the worldwide leading cause of mortality and inflicts a large morbidity burden [1]. Unhealthy dietary habits are a major modifiable risk factor for developing CVD, both independently as well as through a harmful effects on cardiovascular risk factors like blood pressure and low-density lipoprotein cholesterol (LDL-C) levels [2,3].

The Dietary Approaches to Stop Hypertension (DASH) diet is a dietary pattern rich in fruits, vegetables, whole grains, low-fat dairy products and with a focus on plant-based rather than animal protein [4,5]. DASH was originally developed for blood pressure management in people with hypertension, but is nowadays more widely recommended for populations with (high risk of) CVD [6–8]. Although the benefits of the DASH diet with regards to blood pressure and body weight reduction are well established [9–11] there have been no long-term clinical trials that assessed the effects of the DASH diet on risk of (recurrent) cardiovascular events or mortality. In general, randomized controlled trials investigating

Abbreviations: 95%CI, 95% confidence interval; CVD, Cardiovascular disease; DASH, Dietary approaches to stop hypertension; FFQ, Food frequency questionnaire; HR, hazard ratio; ICD, International Classification of Disease; IPTW, Inverse probability of treatment weighting; LDL-C, low-density lipoprotein; MI, myocardial infarction; PS, propensity score; RASi, renin-angiotensin- system inhibitor; SMD, standardized mean difference.

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the long-term effects of dietary interventions on hard clinical endpoints are lacking.

Observational studies on the long-term effects of adhering to the DASH diet have reported mixed results, with some studies showing neutral associations with risk of cardiovascular events and mortality [12–15] while others found protective associations with CVD, cancer and all-cause mortality [16–21]. These studies were performed in the general population or populations at high cardiovascular risk, but not in patients with established CVD. The health consequences of adhering to a DASH diet may be different in a CVD population due to a higher absolute risk of cardiovascular events, a different distribution of cardiovascular risk factors and more prevalent use of lipid-lowering and blood pressure-lowering medications.

Current knowledge about the long-term effects of dietary patterns, such as the DASH diet, on health outcomes is largely based on observational studies, because randomized trials are often considered unpractical, unethical and too costly [22]. Using observational data to estimate causal effects of dietary interventions is subject to bias from selection, information, reverse causation, confounding and confounding by indication [23,24]. Target trial emulation is an increasingly popular methodology that can be used to approximate causal effects in observational data [25–28]. By first designing a target trial that would answer the clinical question and then emulating that trial in observational data, potential sources of bias come to light and can be addressed in the design of the observational study. As a result, the results are more directly applicable in clinical practice [25–28].

The aim of this study was to emulate a clinical trial that assesses the long-term relation compliance with the DASH dietary pattern and risk of cardiovascular and all-cause mortality in patients with a history of myocardial infarction (MI).

2. Material and methods

2.1. Target trial

In brief, the target trial would be a single-blind, randomized controlled trial that would include adults with stable coronary artery disease after having experienced an acute MI. To qualify for participation, the qualifying MI needed to be ascertained by the treating physician based on anginal chest pain, typical changes on the electrocardiogram and/or myocardial enzymes and to have occurred between 6 months and 2 years before inclusion in the trial. All participants need to be 18 years or older and able to give written informed consent.

Eligible participants would be randomized in a 1:1 ratio to the intervention or the control diet. The dietary intervention would be known to participants and their dietary counsellors, but not to investigators assessing or analysing outcome data (investigator-blinded study). The primary outcome of the target trial would be time to cardiovascular death and all-cause death. Table 1 summarizes the design of the target trial and its emulation in the observational data set.

2.2. Trial interventions

Participants of the target trial would be randomly assigned to one of two dietary strategies, which they would be expected to maintain for the duration of the study.

1. No intervention. Participants are expected to have received counselling on healthy dietary habits as part of routine clinical care for MI patients. Participants in this control group receive no additional counselling or support on their dietary habits [7,8].
2. The DASH dietary intervention. A dietary intervention based the DASH intervention arm of previous trials [4,5,29]. This intervention comprises nutritional counselling sessions on a dietary pattern emphasizing fruits, vegetables, whole-grains and low-fat dairy products in lieu of red meats and refined carbohydrates. Participants will be provided with recipes, week menus and shopping lists that are in line with the DASH diet. Food items will not be provided.

2.3. Causal contrast and statistical analysis

The primary outcome, difference in risk of cardiovascular mortality and all-cause mortality, would be assessed using the log-rank test in Kaplan Meier survival analyses. The primary causal contrast of interest would be the intention-to-treat effect, comparing the (cardiovascular) mortality risks of the DASH intervention group to care-as-usual. A per-protocol analysis would be performed as a secondary outcome. Per-protocol analyses may be a useful addition in this setting, especially because of the high attrition rates in dietary intervention trials [30].

2.4. Target trial emulation in observational data

2.4.1. Study population

For the target trial emulation, data from the Alpha Omega Cohort was used. This is a prospective cohort study, comprising adults aged 60–80 years who experienced a MI within ten years before inclusion (2002–2006). During early follow-up, patients were randomized to low-dose supplementation of omega-3 fatty acids or placebo for approximately 40 months, which resulted in no effect on cardiovascular events and all-cause mortality [31]. Therefore randomization was ignored, and the Alpha Omega Cohort was treated like an observational cohort study. Follow-up for cause-specific mortality continued and is still ongoing. The study was approved by the research ethics committee and all participants gave written informed consent. Details on study design and eligibility criteria have been published previously [31,32].

For the present study, patients with missing FFQ data or implausible energy intake (total energy intake <800 kcal/day or >8000 kcal/day for men and <600 kcal/day or >6000 kcal/day for women) were excluded (n = 19, 0.4%), leaving a total of 4365 patients with a history of MI.

At baseline, all participants completed a health questionnaire, physical examination and laboratory measurements. Physical activity was assessed using the validated Physical Activity Scale for the Elderly [33]. Blood pressure was measured two times using an automated device (HEM-711; Omron); the average of the two measurements was used in the analyses. Serum lipids were determined from non-fasting blood and analysed by an automated analyser (Hitachi 912; Roche Diagnostics).

Dietary intake was assessed using a 203-item food frequency questionnaire (FFQ) [34]. The FFQ assessed food and beverage intake over the last month before inclusion. Sodium intake was assessed from food items only and did not include discretionary salt use. Trained dietitians checked all responses and additional data was obtained when responses were missing or unclear. Energy and nutrient intake were calculated by linking the FFQ responses to the Dutch Food Composition Database (2006) [35].

Cardiovascular deaths were coded in accordance with the International Classification of Disease coding, tenth revision (ICD-10) [36] and comprised the following codes: I20–I25, I46, R96, I50 and I60–I69. Data on vital status was obtained through linkage of the Alpha Omega Cohort to municipal registries from baseline through December 2018. Causes of death were obtained from the national

Table 1
Target trial protocol and emulation in the Alpha Omega Cohort.

	Target trial	Emulated trial in observational data
Aim	To estimate the effect of an intervention to improve compliance with the DASH diet on risk of cardiovascular and all-cause mortality in patients with a history of myocardial infarction.	To estimate the effect of compliance with the DASH diet on risk of cardiovascular and all-cause mortality in patients with a history of myocardial infarction.
Eligibility criteria	Male or female (aged 18 years or older). Stable coronary artery disease after having experienced myocardial infarction, defined based on anginal chest pain, typical changes on the electrocardiogram and/or myocardial enzymes. Myocardial infarction should have occurred within 6 months and 2 years before inclusion in the trial. Able to provide written informed consent	Patients, aged 60–80, with a history of myocardial infarction within 10 years of inclusion. Additionally, patients that reported implausible energy intake on a food frequency questionnaire at baseline were excluded.
Sample size	A total of 497 deaths would be needed to detect a hazard ratio of 0.80, with two-sided α of 0.05 and 80% power. This requires a total sample size of 1212 patients, equally distributed over the intervention and control group. The sample size calculation was based on the following assumptions: - 1:1 randomization ratio - Expected effect: HR 0.80 - Two-sided α 0.05, power 80% [21] - Accrual period: 2 years - Trial duration: 10 years - Incidence rate control group: 0.069 deaths/person year (median survival 10 years). - Loss to follow-up during the study period: 20% Sample size calculation was based on estimation on the log-rank test [55].	The same number of events would be required in the observational data if the exposure and control groups were of equal size. After IPTW, intervention and control groups had a size of 596.65 and 3767.17 (1:6.3). For this ratio, a total of 1052 deaths would need to be observed; or a total sample size of 2279. Due to the observational design of the study and the determination of endpoints through linking of the data with municipal registries, the loss to follow-up and censoring rates are lower in the observational study. In the emulated trial this was assumed to be 0%. Note: For the observed effect size of HR 0.90, a sample size of 9768 would be required for an α of 0.05 and power 80%.
Dietary strategies	DASH, as described and trialled previously by Appel et al. [4] and Sacks et al. [5].	We assumed that dietary intake reported in baseline food frequency questionnaires adequately represented the dietary intake during the study period. We assessed compliance with the DASH diet using a score developed by Mellen et al. [37] based on the intake target from the original DASH trials [4,5]. We defined a score of $\geq$5 out of 9 as compliant to DASH. In the target trial the DASH diet would be adopted at the start of the trial. In the emulated trial, the moment of DASH initiation is unknown, but likely to be (long) before inclusion in the observational cohort.
Assignment	Patients are randomly assigned 1:1 to either the intervention or comparator diet.	Randomization not possible, instead was emulated with inverse probability of treatment weighting (IPTW). A propensity score for complying with the DASH diet was constructed using logistic regression models with adjustment for age, sex, education level, smoking status, alcohol consumption, physical activity and creatinine. After IPTW the DASH-compliant and non-compliant groups were balanced in a 1:6.3 ratio.
Outcome	Follow-up starts at inclusion in the trial and ends at death or loss to follow-up, whichever comes first. Intended trial duration would be 10 years.	Follow-up starts at inclusion in the study and ends at death, loss to follow-up, or December 31st, 2018 (the end of follow-up for the Alpha Omega Cohort), whichever comes first A sensitivity analysis with follow-up cut off after 10 years was run to mimic the 10 years follow-up of the target trial.
Follow-up	(Cardiovascular) death after inclusion in the trial	Same
Causal contrast	Intention-to-treat effect	Observational analogue of a per-protocol effect. Intervention strategies cannot be assigned in observational data. It is only possible to present the causal contrast between people that comply with the intervention and those who do not, balanced for observed confounders.
Statistical analysis	Intention-to-treat analysis: unadjusted Cox proportional hazard models to estimate relative risk reductions with the DASH diet.	Unadjusted Cox proportional hazard models in the IPTW pseudo-population to estimate relative risk reductions with compliance with the DASH diet.

Abbreviations: DASH: Dietary approaches to stop hypertension, IPTW: inverse probability of treatment weighting.

mortality registry (Statistics Netherlands, CBS). From 2013, the CBS only provided the primary cause of death and therefore treating physicians were asked to complete an additional cause-of-death questionnaire (response rate 67%).

2.4.2. Modifications to the trial protocol

Eligibility criteria of the observational data were age between 60 and 80 years at the moment of inclusion, which is stricter than the inclusion criterion of an age >18 years in the target trial. Conversely, patients with a MI within the past 10 years were eligible for the Alpha Omega study, which was broader than the time restriction in the target trial. This restriction on time since qualifying event was loosened in the target trial emulation, to maintain sufficient statistical power.

Randomization to the control diet or the dietary intervention could not be applied to patients in the observational dataset. Compliance with the DASH diet was therefore quantified using a DASH diet compliance index proposed by Mellen and colleagues [37]. This diet index comprises nine components: saturated fat, total fat, protein, cholesterol, fibre, magnesium, calcium, potassium and sodium. For each component, a target intake (indexed to total daily energy intake) was proposed based on the target intakes from the two original DASH trials [4,5]. Respondents received 1 point when they achieved the target intake for a DASH component; when only the intermediate target was reached, 0.5 point was awarded. The scores for the nine components were then summed, meaning that a total score ranging between 0 and 9 points could be achieved.

Supplemental table S1 shows the targets and intermediate targets for the nine DASH components.

In the current study, patients were classified with a DASH compliance greater or equal to 5 out of 9 as DASH-compliant. To emulate randomization, a pseudo-population with balanced distribution of confounding factors over the intervention and comparator groups was created, using inverse probability of treatment weighting (IPTW).

2.4.3. Statistical analysis

Continuous baseline characteristics were presented as mean with standard deviation or median with interquartile range, as appropriate. Categorical baseline characteristics were presented as number with percentage.

Real-world compliance with medical treatments or lifestyle behaviours is often motivated by underlying medical conditions, that are also associated with clinical outcomes: *i.e.* confounding by indication [38]. Propensity score (PS) methods, including IPTW, have been suggested as a statistical method to deal with confounding by indication in observational studies [39–41]. A PS was constructed to predict the probability of being DASH-compliant using multivariable logistic regression adjusted for the a priori identified confounders: age, sex, education level, smoking status, alcohol consumption, leisure-time physical activity and serum creatinine level. A pseudo-population was created using IPTW, where patients that were DASH-compliant received a weight of *1/PS* and patients that were not DASH-compliant received a weight of *1/(1-PS)*. IPT weights were stabilized to prevent the impact of outliers. After IPTW, balance was assessed by calculating standardized mean differences (SMD) in baseline characteristics and SMD values < 0.10 were accepted as indicative of achieved balance between the intervention and comparator group [42]. The relation of compliance with the DASH diet with cardiovascular mortality and all-cause mortality risk was assessed using the Kaplan Meier method. Weighted Cox proportional hazard models with time-on-study as a time axis were used to obtain hazard ratios (HRs) for all-cause and cardiovascular mortality in the pseudo-population. Schoenfeld residuals were visually assessed to check the proportional hazard assumption. The IPT-weighted models are presented as the main findings, but explorative adjustments were made for the covariates included in the PS estimation and for covariates that could be either confounder or intermediates, *i.e.* type 2 diabetes, body mass index, systolic blood pressure, LDL-C and high-sensitivity C reactive protein (hsCRP) levels.

Missing data was imputed with single imputation using predictive mean matching. A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using R statistical software, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

2.4.4. Subgroup analyses and sensitivity analyses

Sensitivity analyses with DASH compliance defined as a score ≥2, ≥3, ≥4 and ≥6 were performed to assess the impact of the choice of compliance cut-off. A new PS was estimated for each cut-off and HRs were estimated after IPTW. The IPT-weighted analyses were also repeated in subgroups of patients not currently using any blood-pressure lowering agents (N = 446) and a subgroup of patients not using renin-angiotensin system inhibitors (RASi, N = 3372) to assess potential effect modification by the use of these medications and the DASH diet.

Sodium intake is difficult to assess using FFQs and might be underestimated. Therefore, a sensitivity analysis excluding the sodium criterion from Mellen's proposed DASH compliance scores was performed. In this sensitivity analysis a DASH score ≥4/8 instead of ≥5/9 was defined as DASH compliant. Unweighted, multivariable adjusted Cox proportional hazard models were run as a sensitivity analysis to explore differences in the estimates compared to IPTW, one comparing DASH compliance (score ≥5/9) to non-compliance and one comparing quintiles of the DASH compliance scores.

3. Results

3.1. Baseline characteristics

Table 2 shows the baseline characteristics of 4365 post–MI patients included in the present analysis. Median age was 69 [IQR 64–73] years and the majority of the cohort was male (N = 3,432, 79%). Upon inclusion in the cohort, the median time since the classifying MI was 3.7 years. Over 85% of the cohort was treated with lipid- and/or blood pressure-lowering medications.

DASH compliance scores in the cohort ranged between 0 and 8.5 out of a maximum score of 9, with a median of 3.0 [IQR 2.0–4.0] (Figure S1). DASH compliance scores were higher for women compared with men, but followed similar distributions across strata of age, education, smoking status, alcohol consumption and physical activity level (Figure S1). When focusing on individual components of the DASH compliance score, compliance was high for the fibre and potassium targets, with over 70% of the cohort reaching at least the intermediate intake target level for these components. Compliance was lowest for protein and saturated fat intake, with 73% of the participants not even reaching the intermediate intake target (Figure S2).

Five hundred ninety-eight participants (14%) had a DASH compliance score ≥5 and were classified as DASH-compliant. Patients that were DASH-compliant were similar in age, history of diabetes, physical activity level and education levels compared with those that were not. However, DASH-compliant patients were more frequently female (40% vs 18%) and less frequently smokers (10% vs 17%). SMD values in the unadjusted data indicated that the DASH-compliant and non-compliant groups were not balanced (Table 2). After IPTW was applied, the baseline characteristics and potential confounding covariates were balanced over the DASH-compliant and non-compliant groups (Table 2, Figure S3).

3.2. Relation with cardiovascular mortality and all-cause mortality

During a median follow-up of 12.4 years, 2035 deaths occurred of which 903 (44%) were of cardiovascular origin. Figure 1 shows IPT-weighted Kaplan Meier curves for all-cause mortality and cardiovascular mortality. DASH compliance showed no association with all-cause mortality (HR 0.92, 95%CI 0.80–1.06) and cardiovascular mortality (HR 0.90, 95%CI 0.72–1.11). Further adjustments for potential confounders and intermediate factors did not affect the estimates (Table 3).

In a sensitivity analysis using multivariable adjusted Cox proportional hazard models, instead of IPT-weighted Cox models, the direction and size of the relations between DASH compliance and all-cause and cause-specific mortality were similar to the main analyses (HR 0.91, 95%CI 0.80–1.04 and HR 0.87, 95%CI 0.71–1.06 respectively (Table S2).

Figure 2 shows the IPT-weighted and multivariable adjusted HRs for different cut-off values for DASH compliance. IPTW was successful for the alternative cut-off values, and balance of baseline characteristics (SMDs <0.10) was achieved at each threshold (data not shown). Both lower (≥2, ≥3, ≥4 of 9) and higher (≥6 of 9) cut-off values for DASH compliance were not related with a significantly reduced risk of all-cause and cardiovascular mortality. In sensitivity analyses assessing DASH compliance in quintiles of the compliance distribution, there was no indication of a

Table 2
Baseline characteristics of the Alpha Omega cohort – overall and stratified for DASH compliance, before and after IPTW.

	Full cohort	Study population before IPTW			Pseudo-population after IPTW		
		Not DASH-compliant	DASH-compliant	SMD	Not DASH-compliant	DASH-compliant	SMD
N	4365	3767	598		3767.17	596.65	
Age, *year*	69 [64–73]	69 [64–73]	69 [65–74]	0.062	69 [64–73]	69 [65–73]	0.025
Male sex, *N (%)*	3432 (79)	3071 (82)	361 (60)	0.479	2961.6 (79)	468 (78)	0.004
Education, *N (%)*				0.036			0.016
Low	888 (20)	773 (21)	115 (19)		767.0 (20)	124.4 (21)	
Lower-Middle	1566 (36)	1345 (36)	221 (37)		1350.4 (36)	213.0 (36)	
Middle-High	1376 (32)	1188 (32)	188 (31)		1187.9 (32)	185.0 (31)	
High	535 (12)	461 (12)	74 (12)		461.8 (12)	74.3 (13)	
Diabetes mellitus, *N (%)*	883 (20)	744 (20)	139 (23)	0.085			0.089
Smoking status, *N (%)*				0.326			0.009
Never	723 (17)	570 (15)	153 (26)		623.7 (17)	98.3 (17)	
Former, quit >10 years ago	767 (18)	656 (17)	111 (19)		662.5 (18)	105.3 (18)	
Former, quit ≤10 years ago	2162 (50)	1885 (50)	277 (46)		1865.7 (50)	297.4 (50)	
Current	713 (16)	656 (17)	57 (10)		615.3 (16)	95.7 (16)	
Alcohol consumption, *glasses/wk*	5 [2–12]	6 [2–12]	4 [1–9]	0.297	5 [2–12]	5 [2–12]	0.016
Physical activity level, *METh/wk*	23 [11–45]	23 [11–45]	24 [11–47]	0.037	23 [10–45]	24 [11–45]	0.009
Body mass index, *kg/m2*	27.7 ± 3.8	27.7 ± 3.8	28.1 ± 3.9	0.091	27.7 ± 3.8	28 ± 3.8	0.065
Waist circumference, *cm*	102 ± 10	102 ± 10	101 ± 11	0.156	102 ± 10	102 ± 11	0.008
Systolic blood pressure, *mmHg*	142 ± 22	142 ± 22	143 ± 21	0.036	142 ± 22	143 ± 21	0.055
Diastolic blood pressure, *mmHg*	80 ± 11	80 ± 11	80 ± 11	0.068	80 ± 11	80 ± 11	0.003
Total cholesterol, *mmol/L*[a]	4.6 [4.0–5.3]	4.6 [4.0–5.3]	4.7 [4.0–5.3]	0.047	4.6 [4.0–5.3]	4.6 [4.0–5.3]	0.015
Triglycerides, *mmol/L*[a]	1.7 [1.2–2.3]	1.7 [1.2–2.3]	1.7 [1.2–2.3]	0.015	1.7 [1.2–2.3]	1.7 [1.2–2.3]	0.003
HDL-cholesterol, *mmol/L*[a]	1.2 [1.0–1.5]	1.2 [1.0–1.5]	1.3 [1.1–1.5]	0.099	1.2 [1.1–1.5]	1.2 [1.0–1.5]	0.016
LDL-cholesterol, *mmol/L*[a]	2.5 [2.0–3.0]	2.5 [2.0–3.0]	2.5 [2.0–3.0]	0.008	2.5 [2.0–3.0]	2.5 [2.0–3.0]	0.015
Creatinine, *μmol/L*	86 [75–99]	86 [75–99]	83 [72–96]	0.171	86 [75–99]	86 [75–98]	0.011
High sensitivity CRP, *mg/L*	1.7 [0.8–3.8]	1.7 [0.8–3.8]	1.7 [0.8–3.7]	0.069	1.7 [0.8–3.8]	1.7 [0.8–3.7]	0.047

Baseline characteristics of the overall Alpha Omega cohort and stratified for DASH compliance, defined as a score ≥5/9, before and after IPTW.IPTW was based on a propensity score adjusted for, sex, education, smoking, alcohol consumption and creatinine. Data are presented as N (%) for categorical variables and as mean ± standard deviation or median [interquartile range] for continuous variables. **Abbreviations:** DASH: Dietary approaches to stop hypertension, HDL: High density lipoprotein, LDL: Low density lipoprotein, CRP: C reactive protein., IPTW: inverse probability of treatment weighting, SMD: standardized mean difference.
[a] Non-fasting measurements.

dose–response relation between DASH compliance score and all-cause or cardiovascular mortality (Figure S4).

To more closely mimic the target trial, a sensitivity analysis was performed limiting the follow-up to 10 years, after which patients that were still alive were censored. In this analysis, the incidence rates for all-cause mortality and cardiovascular mortality did not differ according to DASH compliance status ((all-cause mortality: 3.4/100 py for non-DASH compliant versus 2.9/100 py for DASH-compliant patients and cardiovascular mortality: 1.6/100 py vs. 1.4/100 py, respectively (Table S2)).

In an IPT-weighted sensitivity analysis that negated the sodium component of the DASH compliance score, similar HRs were found compared to the main analysis (Table S2). In hypothesis-generating analyses of patients not using any blood pressure-lowering agents (N = 446), a protective association of DASH compliance and all-cause mortality (HR 0.85, 95%CI 0.45–1.63) and cardiovascular mortality (HR 0.36–1.12) was found (Table S2). In patients not using any RASi a smaller but still protective association was found (Table S2).

4. Discussion

In this study, a target trial was emulated to assess of the relationship between DASH compliance and risk of (cardiovascular) mortality in an observational cohort of patients with a history of MI. Adhering to the DASH diet was not related with reduction in cardiovascular and all-cause mortality risk in a population with established CVD. This absence of a beneficial relationship may in part be explained by a high proportion of patients using blood-pressure lowering agents which interfere with the working mechanisms of the DASH diet.

It is not possible to compare the findings of the present study to experimental study data, as no such long-term RCT on the clinical effects of DASH has ever been performed in a population with CVD, or any other population. A meta-analysis of observational studies in apparently healthy patients reported a pooled estimate of 20% relative risk reduction for both all-cause and cardiovascular mortality when comparing the highest to lowest DASH compliance categories [21]. Effect estimates in the present study were smaller, probably due to smaller contrast between the DASH-compliant and non-compliant participants or because the meta-analysis did not include secondary prevention populations. Overall, the findings in the current study are in line with existing literature that shows that compliance with the DASH diet has a small, if any, effect on cardiovascular and all-cause mortality risk [12–21].

Previous short-term RCTs in populations at high cardiovascular risk, found that DASH effectively reduces body weight [11,43] and blood pressure [5,29,44], and observational studies in these populations indicate that DASH also has a beneficial association with cardiovascular and mortality outcomes, possibly through amelioration of cardiovascular risk factors [16–21]. However, body weight reduction and blood pressure-lowering effects were not observed in the present study. DASH has been hypothesized to reduce blood pressure through reduced sodium intake, additional natriuretic effects [45], and inhibition of RAS which induces a blood pressure-lowering response [46,47]. The blood pressure-lowering potential of DASH in the study population will likely have been limited because a vast majority of the Alpha Omega Cohort, was treated with blood-pressure lowering agents, some of which also interact with RAS. This hypothesis is supported by the larger benefits observed in subgroups of patients not using any blood pressure-lowering agents or RASi specifically. These findings suggest that the use of such agents may attenuate the effects of the DASH diet.

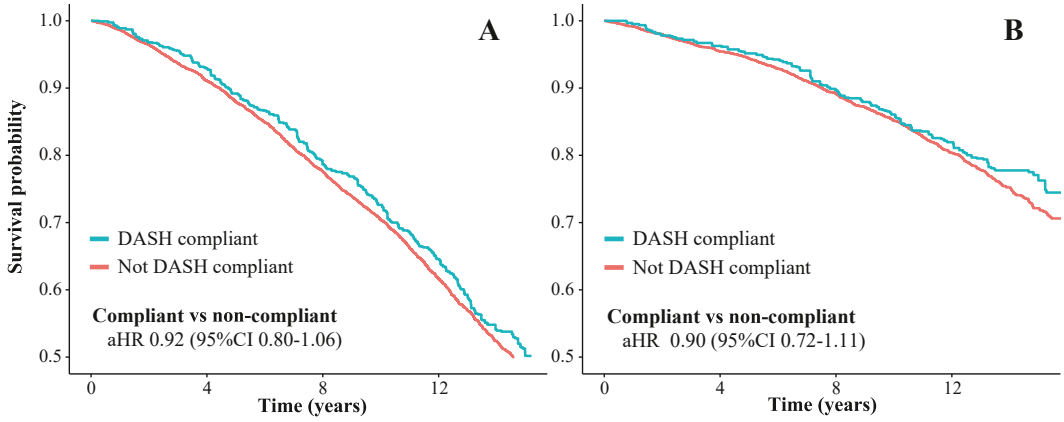

Fig. 1. IPT-weighted Kaplan Meier curves for all-cause mortality and cardiovascular mortality. Propensity score-matched Kaplan Meier curves for all-cause mortality (A) and cardiovascular mortality (B). The presented hazard ratios are based on IPT-weighted Cox proportional hazard models. **Abbreviations**: 95%CI: 95% Confidence Interval, HR –Hazard Ratio, DASH: Dietary Approaches to Stop Hypertension.

Table 3
IPTW estimates for the effect of DASH compliance on the risk of all-cause and cardiovascular mortality.

	All-cause mortality		Cardiovascular mortality	
	Not DASH-compliant	DASH-compliant	Not DASH-compliant	DASH-compliant
Crude	*Reference*	0.92 (0.80–1.06)	*Reference*	0.90 (0.72–1.11)
Model 1	*Reference*	0.89 (0.77–1.03)	*Reference*	0.88 (0.70–1.09)
Model 2	*Reference*	0.89 (0.77–1.02)	*Reference*	0.87 (0.70–1.08)

The crude model included no covariates but was IPT-weighted. Model 1 adjusted for the confounders included in the propensity score model: age, sex, education, smoking and alcohol consumption. Model 2 was further adjusted for body mass index, systolic blood pressure, LDL-cholesterol and type 2 diabetes.
Abbreviations: DASH: Dietary approaches to stop hypertension.

Table 4
Sensitivity analysis – Effect estimates based on multi-variable adjusted Cox regression models.

	All-cause mortality		Cardiovascular mortality	
	Not DASH-compliant	DASH-compliant	Not DASH-compliant	DASH-compliant
Events/N	1774/3767	261/598	789/3767	114/598
FU (py)	41,583	6891	41,583	6891
Crude	*Reference*	0.87 (0.77–0.99)	*Reference*	0.86 (0.71–1.04)
Model 1	*Reference*	0.92 (0.80–1.05)	*Reference*	0.88 (0.72–1.08)
Model 2	*Reference*	0.91 (0.80–1.04)	*Reference*	0.88 (0.72–1.07)

Hazard ratios for compliance with the DASH-diet and risk of all-cause mortality and cardiovascular mortality estimated using multivariable-adjusted Cox Proportional Hazard models. Model 1 adjusted for the confounders included in the propensity score model: age, sex, education, smoking, alcohol consumption, physical activity and creatinine. Model 2 further adjusted for body mass index, systolic blood pressure, LDL-cholesterol and type 2 diabetes.
Abbreviations: DASH: Dietary approaches to stop hypertension, py: person year.

Overall, the target trial emulation was successful. Important design components of the target trial that could not directly be emulated in the observational study were age of the study population and time since the qualifying MI. As a result, the emulated trial comprised an older population with a relatively long time since the qualifying event. This may have resulted in an attenuated relation between DASH compliance and (cardiovascular) mortality, because the benefits of dietary changes likely take a few years to fully manifest and may therefore be more pronounced in younger populations [48]. Furthermore, people were not actively instructed to adopt a DASH diet, but instead they were naturally compliant to the diet. Previous studies suggest that DASH's blood pressure-lowering effects manifest quickly, even as soon as one or two weeks after diet initiation, and remain stable afterwards [4,49,50]. The observation that the HRs for DASH compliance in the present study were not statistically significant might have been due to insufficient statistical power, as a post hoc power calculation indicated that approximately 10,000 participants would have been required to detect a statistically significant result for a HR of 0.90.

4.1. Strengths and limitations

Strengths of the current study include the extensive range of available baseline characteristics which were systematically collected. Linkage with mortality registries prevented loss to follow-up and limited the chance of selection bias introduced by informative censoring [27,51,52]. This study is the first target trial emulation to assess the long-term relation of DASH compliance with (cardiovascular) mortality risk. Using target trial has resulted in a well-defined study population, which improves applicability of the findings to external populations. Moreover, using IPTW is a recommended statistical approach to handle confounding by indication [39–41] and yielded a well-balanced distribution of confounders over the intervention and reference group.

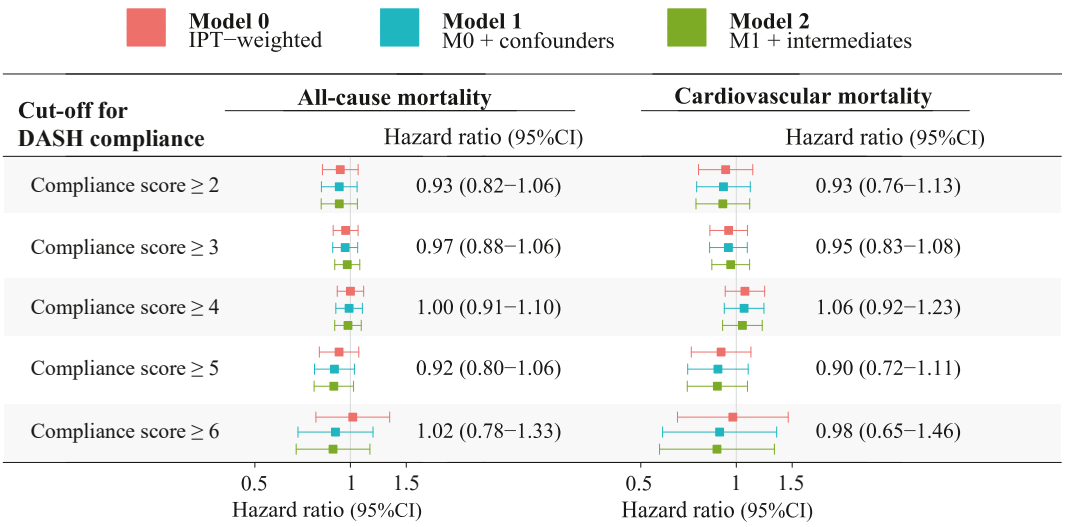

Fig. 2. IPT-weighted hazard ratios for alternative cut-offs for DASH compliance. This figure shows the estimated hazard ratio for all-cause and cardiovascular mortality for alternative cut-offs for DASH compliance. For all included cut-offs, patients with a score greater or equal to the cut-off value are compared with patients below the threshold. The presented numerical hazard ratios are IPT-weighted; a new propensity score was calculated for each cut-off value. The forest plot shows the IPT-weighted hazard ratio, model 1 is a hazard ratio that was further adjusted for confounders: age, sex, education, smoking and alcohol consumption. Model 2 was additionally adjusted for body mass index, systolic blood pressure, LDL-cholesterol and type 2 diabetes (potential confounders or intermediates). **Abbreviations:** IPT: inverse probability of treatment, 95%CI: 95% confidence interval.

Study limitations need to be considered. The current study did not actively randomize patients to be DASH-compliant or non-DASH compliant and is remains observational research. Using trial emulation and IPTW techniques, does not resolve all biases that are inherent to observational research, such as unmeasured confounding, model misspecification and measurement bias. In these analyses, no adjustments could be made for variables that were not measured, but which might have affected the findings (e.g. frailty and functional status). For the determination of dietary intake, we relied on self-report in an FFQ, which, although validated in a Dutch population [34], is sensitive to measurement and reporting errors. Reduction of sodium intake is an important aspect of the DASH diet, but it is notoriously difficult to validly estimate using an FFQ [53]. Estimated sodium intake was relatively low in this cohort compared with the Dutch population but could have been underestimated [54]. Misclassification of sodium intake could have diluted the observed associations with compliance with DASH, but a sensitivity analysis excluding the sodium criterion yielded highly similar results to the main analysis. Dichotomization of the DASH compliance score into compliant and non-compliant categories is likely to have resulted in loss of contrast and an underestimation of the true effect size of a DASH intervention. However, in an analysis of DASH compliance quintiles, no indication for a dose−response relation was found.

Using explicit trial emulation and IPTW reduced the risk of biases and increased transparency of the findings but did not eradicate all biases that accompany observational data when answering etiologic questions. Ideally, a long-term RCT would be performed to assess the benefits of the DASH diet in an experimental setting. As it is unlikely that such a trial will ever be performed, the present study provides an important clue that the DASH diet is unlikely to have large beneficial effects in patients with established CVD.

5. Conclusion

In conclusion, this target trial emulation assessing the relationship between compliance with the DASH diet and all-cause and cardiovascular mortality found no association between compliance with the DASH diet and reductions in risks of all-cause and cardiovascular death. This survival benefits effectuated by the DASH diet can partly be explained by the high proportion of CVD patients treated with blood-pressure lowering medications that modify the effect of the DASH diet.

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Author contributions

NEB: Conceptualization, Formal analysis, Writing - Original Draft, Visualization, EC: Writing - Review & Editing, FLJV: Conceptualization, Writing - Review & Editing, Supervision, YTvdS: Writing - Review & Editing, JMG: Resources, Writing - Review & Editing, Supervision, CK: Conceptualization, Writing - Review & Editing, Supervision.

Data availability statement

Data described in the manuscript, codebook, and analytic code will be made available upon request pending application and approval.

Conflict of Interest

The authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.06.033.

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