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The association of the Mediterranean diet with heart failure risk in a Dutch population

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Abstract *Background and aims:* It is still unclear whether a healthy diet can prevent heart failure (HF). Therefore, this study aimed to investigate the association between adherence to a Mediterranean-style diet, reflected by modified Mediterranean Diet Scores (mMDS), and the incidence of HF in men and women.

Methods and results: This observational study comprised 9316 men and 27,645 women from the EPIC-NL cohort free from cardiovascular disease at baseline. Dietary intakes were assessed using a validated food frequency questionnaire. mMDS was calculated using a 9-point scale based on consumption of vegetables, legumes, fruit, nuts, seeds, grains, fish, fat ratio, dairy, meat and alcohol. HF events were ascertained by linkage to nation-wide registries. Multivariable Hazard Ratios (HR) and 95% confidence intervals (CI) were estimated by Cox proportional hazards regression models.

Over a median follow-up of 15 years (IQR 14–16), 633 HF events occurred: 144 in men (1.5%) and 489 in women (1.8%). The median mMDS was 4 (IQR 3–5). There was significant effect modification by sex (P-value for interaction <0.001), therefore results are stratified for men and women. For men, a higher mMDS associated with lower HF risk (HR: 0.88; 95% CI: 0.79, 0.98 per point increase in mMDS; HR upper category: 0.53; 95% CI: 0.33, 0.86), whereas no association was found in women (HR: 0.98; 95% CI: 0.93, 1.04 per point increase; HR upper category: 1.07; 95% CI: 0.83, 1.36).

Conclusion: Adherence to a Mediterranean-style diet may reduce HF risk, particularly in men. The underlying reasons for the differences in findings between men and women need further study.

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Introduction

Heart failure (HF) is considered to be a major public health issue, because of its high prevalence, and related high rates of mortality and healthcare costs [1].

HF is defined as an abnormality of cardiac structure or function [2]. HF is commonly divided into two subtypes. In HF with preserved ejection fraction (HFpEF) is the diastolic function impaired. HFpEF is most common in women, with hypertension as the most important risk factor, followed by obesity and diabetes. In HF with reduced ejection fraction (HFrEF) is the systolic function impaired, due to hypertrophy [2]. HFrEF is most common in men, especially for those who have a history of smoking or myocardial infarction (MI) [3].

Suppressing the risk factors for HF could potentially reduce the number of future HF patients. The World Health Organization estimated that three-quarter of deaths due to cardiovascular diseases (CVD), including HF, could be prevented by controlling lifestyle risk factors such an unhealthy diet [4]. However, studies on the potential of controlling dietary intake, such as with a Mediterranean-style diet that has been shown protective against CVD in general [5], for specifically the primary prevention of HF have shown inconsistent results [6–11].

The Mediterranean diet is characterized by high monounsaturated/saturated fat ratios, with olive oil as the main source of fat; high consumption of vegetables, fruits, legumes, and cereal products; moderate consumption of wine and dairy products; and low consumption of red and processed meat [12]. Two Swedish prospective cohort studies and an Italian case-control study confirmed a Mediterranean style diet to be of importance for HF prevention [7–9]. However, secondary analyses in de PREDIMED study and a German cohort study did not confirm this since both found no relationship of Mediterranean-style diet adherence with HF risk [10,11].

The purpose of this study was to further elucidate whether a Mediterranean-style diet is associated with incident HF in middle-aged men and women. For this, we used the European Prospective into Cancer and Nutrition – Netherlands (EPIC-NL) cohort.

Methods

Study population

EPIC-NL consists of the Prospect- and MORGEN-cohorts that cover the Dutch contribution to EPIC. The Prospect-EPIC study includes 17,357 women, aged 49–70 y at baseline, who participated in the national breast cancer screening program and living in the city of Utrecht and its surroundings. The MORGEN-EPIC cohort consists of 22,715 men and women aged 21–64 y based on an age and sex stratified random sample of inhabitants from 3 towns in the Netherlands (Amsterdam, Doetinchem, and Maastricht) [13]. Both cohorts were set up between 1993 and 1997, and merged into one cohort in 2007. All participants signed informed consent prior to study inclusion. Both cohorts were approved by local medical ethics committees. Participants who withdrew permission for inclusion in the study (n = 1), without permission for linkage to disease registries (n = 1756), with prevalent CVD (n = 546), failure to report dietary intake (n = 171), extreme dietary intake (lowest and highest 0.5% of the ratio of energy intake over basal metabolic rate) (n = 349), and with missing data on educational level (n = 194), and smoking status (n = 33) were excluded, leaving 36,961 for the present analysis (Fig. 1).

Baseline data collection

Data on demographic characteristics, presence of chronic diseases, cardiovascular risk factors and physical activity were obtained at baseline with self-administered questionnaires. Physical activity was measured using a questionnaire and was categorized according to the Cambridge Physical Activity Index (CPAI) [14]. A physical examination including body weight, waist and hip circumference and blood pressure (BP) measurement was performed and blood samples were drawn. Systolic and diastolic BP were measured in supine position twice using a Boso-oscillomat (in Prospect) or using a random zero Sphygmomanometer (in MORGEN). Body weight was measured in light indoor clothing without shoes to the nearest 0.5 kg with a floor scale. Body mass index was calculated as weight divided by height squared (kg/m2) [13]. Hypertension was defined as one or more of the following criteria: diastolic BP $\geq$ 90 mmHg, systolic blood pressure $\geq$ 140 mmHg, self-reported antihypertensive medication use, or self-reported presence of hypertension. Total cholesterol was measured using enzymatic methods, and low-density lipoprotein (LDL)-cholesterol and high-density lipoprotein (HDL)-cholesterol were measured using a homogeneous assay with enzymatic endpoint. Cholesterol ratio (mmol/l) was calculated by dividing total by HDL-cholesterol [13].

Food intake and Mediterranean Diet Score

Food intake at baseline was assessed using a semi-quantitative FFQ [15], which was validated against 12 24-h recalls [15]. The validity, expressed in correlation coefficients, varied for men from 0.32 for fish to 0.74 for alcohol and for women from 0.31 for vegetables to 0.87 for

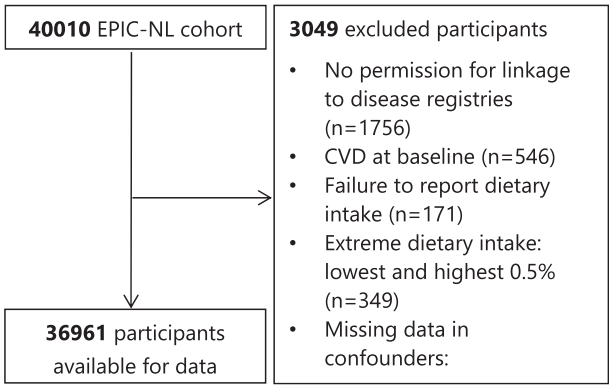

Figure 1 Flowchart describing the selection of study participants.

alcohol [15]. To measure adherence to the Mediterranean diet within the study population, a scale created by Trichopoulou et al. was used [14]. This scale uses sex-specific medians among the participants as cut-off values for the dietary components. Participants with a higher consumption than the sex-specific median for beneficial components (vegetables, fruits, legumes, whole grains, fish, fat ratio (monounsaturated fat + polyunsaturated fat)/saturated fat) received one point and consumption below the median received zero points. For detrimental components (meat, dairy) the reverse was applied. Alcohol was assigned as being beneficial within a range of 10 g/d and 50 g/d for men and 5 g/d and 25 g/d for women [16]. Within this range one point was received and outside this range zero points. Adding up these points, a modified Mediterranean Diet Score (mMDS) from zero (minimal adherence) to nine (maximal adherence) could be obtained that represented the Mediterranean diet adherence per participant at baseline [17]. The score is modified since we used the ratio of mono-plus polysaturated fat and saturated fat whereas the original score used the ratio of mono-saturated fat and saturated fat [14,18]. This deviated the Mediterranean diet score on one point from the original Mediterranean diet score [18].

Ascertainment of HF events

Hospitalization for and death from HF were used to define HF incidence. Hospitalization for HF was determined based on both primary and secondary hospital discharge diagnoses which were obtained from the Hospital Discharge Register (ICD9-code: 428). A primary hospital diagnosis was defined as the underlying disease for hospitalization. A secondary hospital diagnosis was defined as a comorbidity of the primary hospital admission. Vitality information was obtained through the municipal registry and causes of death were obtained from the Cause of Death Register at Statistics Netherlands (ICD10-code: I50). Death from HF was based on both primary and secondary causes of death. Participants were followed up to the date of HF diagnosis, death, or end of follow-up. For this study, information on hospital diagnosis was available until December 31st, 2010. Follow-up was complete until December 31st, 2010. The information obtained from registries lacked the level of detail to allow discriminate on HF subtypes (HFrEF and HFpEF).

Statistical analysis

All data was analyzed using SPSS Statistics for Windows, version 25.0.0.2. Participants were split into four mMDS quartiles: quartile 1 (mMDS 0,1,2,3); quartile 2 (mMDS 4); quartile 3 (mMDS 5); quartile 4 (mMDS 6,7,8,9), with the lowest category reflecting lowest and the highest category reflecting highest adherence. Baseline characteristics were presented by mMDS categories and sex, as percentages for categorical variables and as means (SD) and medians (IQR) for continuous variables.

Cox regression survival analysis was used to estimate the multivariable hazard ratios (HR) and 95% confidence intervals (CI) for the association of the MDS per point increase, and in four categories (using the lowest category as reference group), with HF incidence. Durations of follow-up were calculated from the data of inclusion until the date of HF diagnosis, death, or end of follow-up, whichever came first. Interactions between mMDS and sex were analyzed, by adding product terms to the Cox regression model, to determine if men and women should be analyzed separately. The analyses were adjusted for possible confounders previously described in literature, including age, education level (low, medium, high), smoking status (never, in the past, current smoker), total energy intake (kilocalories), and physical activity (inactive, moderately inactive, moderately active, active). All analyses were stratified by cohort (MORGEN, Prospect), by including cohort in the stratum statement. P-values for linear trend were calculated by including median values of each category of the mMDS in the regression model.

We checked the Cox proportional hazards assumption by visually inspecting log−log plots and observed no deviation from the assumption.

Sensitivity analyses

Five additional analyses were performed with modeled per point increase. First, to avoid impact of possible reverse causation on the results, the association of mMDS and HF was analyzed excluding the HF cases registered within two years after baseline.

Second, we repeated the analyses after adding presence of type 2 diabetes, hypertension, and cholesterol ratio to the multivariable adjusted model. These variables could influence the association of mMDS and HF, but it is debatable whether these variables can be considered confounders or intermediates.

Third, we repeated the analysis after additionally adjusting for BMI.

Fourth, the impact of each separate mMDS component on the association of the overall mMDS with HF was examined. An analysis was performed where the 10-point scale mMDS was altered into a 9-point scale mMDS (0−8) by excluding the mMDS components one by one (MDS minus vegetables; mMDS minus legumes; etcetera).

Fifth, we repeated the analyses with an adapted version of mMDS to further optimize comparability of our study with previous studies. The definition and classification (i.e. protective versus harmful component) of dairy products in mMDS differs between studies; [7,8,10] therefore we additionally calculated the mMDS with fermented dairy (sum of yogurt, buttermilk and cheese) instead of total dairy, and classified as protective instead of harmful component.

Sixth, we repeated the analyses after exclusion of participants with extremely low (MDS of 0) or high (MDS of 9) values of mMDS to address the impact of potential outliers on the associations.

Results

Within this study population, 25% was male. Women (51 ± 11 years) were older than men (43 ± 11 years) (Table 1). The median overall mMDS was 4 (IQR 3–5) for both men and women. In all mMDS categories, women consumed respectively more vegetables, fruits, nuts and seeds, grains and dairy and less meat and alcohol than men. The percentage of non-smokers, highly educated people, physical active people and the energy intake increased with increasing mMDS. Hypertension, cholesterol ratio, diabetes and systolic blood pressure were slightly lower with increasing mMDS (Table 1).

During a median follow-up of 15 years (IQR 14–16), 633 HF events occurred, of which 144 in men (1.5%) and 489 in women (1.8%) (Table 2). The association between the mMDS and HF risk was significantly modified by sex (P-value for interaction <0.001), and therefore, the analysis was conducted for men and women separately. For men, the multivariable adjusted risk of HF was significantly reduced with 12% per mMDS increment (HR: 0.88; 95% CI: 0.79–0.98). For women no association was found (HR: 0.98 95% CI: 0.93–1.04 per mMDS increment). In men, the analysis using categories of mMDS showed a rather similar pattern compared to the continuous analyses, with higher scores associating to reduced HF risks. For women, we found an inverse association in the third category whereas no association was found in the upper, fourth category compared to the first. Survival curves for men and women are additionally presented in Supplementary Figs. 1 and 2.

Sensitivity analyses

Excluding HF participants diagnosed within two years after baseline (32 HF cases) did not materially change the results. The addition of type 2 diabetes, hypertension, and cholesterol ratio as well as the addition of BMI to the multivariable adjusted model, resulted in a minimal attenuated association for women and for men it did not affect the results (Supplementary Table 1). After the exclusion of each separate Mediterranean diet component from the total mMDS, the association was attenuated to non-significance for men, after excluding whole grains, meat and alcohol, and strengthened after excluding fish (Supplementary Table 2). Additional analyses including fermented dairy as beneficial component of mMDS slightly attenuated the associations. Moreover, excluding participants with extremely low or high mMDS did not materially change the results (Supplementary Table 1).

Discussion

Our study shows that higher adherence to a Mediterranean-style diet, as indicated by a relatively higher mMDS, was not associated with risk of HF in women, and with a 12% lower risk per point increment in mMDS in men.

For men, the direction and magnitude of the result is in line with a prior study among Swedish men showing a 15% reduced risk of HF per point increment in the modified MDS (mMDS; this is an mMDS with a slightly different definition compared to the mMDS used in our study, further explained below) [8]. Our result also corresponds with a meta-analysis of overall cardiovascular health, showing two-point increment in an 18-point MDS is associated with a 10% reduced risk of CVD [19].

For women, we did not detect a significant reduced risk of HF with increasing mMDS, which is not in line with prior research of a Swedish cohort of women that observed 6% HF risk reduction per point increment in mMDS [7]. The Swedish study (32,921 women) and our study (27,645 women) used a similar study approach, although the Swedish study used a slightly different approach for calculating the mMDS, with the most striking deviation from our approach being fermented dairy included as beneficial component, whereas the original MDS includes total dairy, classified as harmful component. However, including fermented dairy as beneficial component in the mMDS of our study did not materially change the findings, and therefore this is unlikely an explanation for the differences between studies. Second, differences in cut-offs for beneficial alcohol use are striking, with the mMDS used in the Swedish study having lower upper cut-offs for beneficial alcohol consumption. The cut-offs used in our study may be rather high to indicate beneficial alcohol consumption [20]. However, removing alcohol from the score did not materially change our findings in women. Alternatively, the background diet of the Swedish women regarding fruit and vegetable consumption may have contributed to the differences in findings. The fruit plus vegetable consumption of these women was much higher and had more variation than in our study. We should also note an inverse association with HF was found in category 3 of mMDS for women in our study, but not in the category reflecting highest adherence (category 4). Comparison of women's baseline characteristics between category 3 and 4 showed no striking differences between the two groups, and exclusion of women with extremely low or high mMDS scores did not change the findings. Also, additional (not shown) analyses with mMDS in 10 categories (i.e. each score as a separate category) showed a striking drop of HR for women with an mMDS score of 5 only. In comparison, among men, a gradual decrease in HR was seen over the 10 categories. There is no biological explanation for the inverse association with an mMDS of 5 among women, and we should be careful not to over interpret this finding. Rather, potential causes for differences in mMDS and HF associations between men and women, such as differences in underlying subtypes of HF, should be explored further, as is discussed in more detail below.

Further comparison with prospective studies comes from the German EPIC-Potsdam study and PREDIMED trial that both found no association of MDS with HF risk in study populations of combined men and women [10,11]. The method used in the German cohort study to score MDS was very comparable to ours. The HRs in both studies were in inverse direction, comparable to the Swedish studies and our finding in men [8]. The lack of sex-stratified analyses hampers comparability with the other studies, including the current work.

Table 1 Participants' characteristics at baseline by modified Mediterranean diet score (mMDS) category and sex, in the EPIC-NL Study.

Characteristics	Total population				Men				Women			
Category	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
mMDS range	0–3	4	5	6–9	0–3	4	5	6–9	0–3	4	5	6–9
Subjects, N	11,264	8501	8200	8996	2588	2162	2110	2456	8676	6339	6090	6540
Socio-demographic												
Age at enrollment (years), mean ± SD	50 ± 12	49 ± 12	49 ± 12	49 ± 11	43 ± 11	43 ± 11	43 ± 11	43 ± 11	52 ± 12	52 ± 12	51 ± 11	50 ± 11
High educational level, %	13	18	22	29	20	25	29	35	11	16	20	27
Lifestyle												
Current smokers, %	33	31	29	28	40	38	37	37	31	29	25	25
Physically active[a], %	39	41	43	45	43	44	47	48	38	40	42	44
Body mass index, mean ± SD	26 ± 4	26 ± 4	26 ± 4	25 ± 4	26 ± 4	26 ± 4	26 ± 3	25 ± 3	26 ± 4	26 ± 4	26 ± 4	25 ± 4
Daily intake, median (interquartile range)												
Energy (kcal/day)	1869 (1563–2276)	1950 (1618–2355)	1990 (1655–2417)	2027 (1699–2461)	2455 (2087–2901)	2470 (2096–2946)	2535 (2166–3015)	2578 (2180–3052)	1758 (1495–2058)	1827 (1551–2136)	1852 (1562–2172)	1884 (1612–2167)
Vegetables (gram/day)	87 (66–110)	99 (75–130)	111 ± (85–144)	129 (102–164)	76 (56–97)	87 (66–114)	99 (72–127)	116 (90–144)	90 (69–113)	104 (79–135)	116 (90–149)	135 (108–171)
Legumes (gram/day)	24 (15–35)	28 (17–41)	30 (20–44)	34 (23–47)	22 (13–34)	27 (17–40)	30 (18–44)	36 (25–49)	24 (15–35)	28 (18–41)	30 (20–44)	33 (23–46)
Fruit, nuts and seeds (gram/day)	131 (81–232)	158 (102–260)	197 (121–291)	244 (138–323)	98 (50–146)	126 (66–222)	140 (86–250)	175 (113–264)	139 (98–243)	183 (119–270)	231 (128–309)	253 (163–348)
Whole grains (gram/day)	39 (3–98)	64 (7–108)	69 (12–128)	91 (27–138)	31 (3–110)	39 (5–132)	59 (8–146)	91 (19–178)	45 (3–97)	65 (9–104)	71 (14–117)	92 (32–132)
Fish and seafood (gram/day)	4 (1–8)	7 (3–14)	9 (4–16)	14 (8–18)	4 (2–8)	7 (3–14)	8 (3–14)	13 (8–17)	4 (1–8)	7 (3–14)	9 (4–16)	14 (8–18)
Saturated fatty acids (gram/day)	31 (25–39)	31 (24–39)	30 (24–38)	29 (23–37)	39 (32–48)	38 (31–48)	38 (30–47)	36 (29–45)	30 (24–36)	29 (23–36)	28 (22–35)	27 (21–34)
Unsaturated fatty acids[b](gram/day)	39 (31–50)	41 (32–52)	42 (33–53)	44 (34–55)	52 (42–64)	53 (42–65)	54 (44–67)	56 (45–69)	36 (29–45)	38 (30–47)	39 (31–48)	40 (32–49)
Fat ratio[c] (gram/day)	1.2 (1.1–1.4)	1.3 (1.2–1.5)	1.4 (1.3–1.6)	1.5 (1.4–1.7)	1.3 (1.2–1.4)	1.4 (1.3–1.5)	1.5 (1.3–1.6)	1.5 (1.4–1.7)	1.2 (1.1–1.3)	1.3 (1.2–1.5)	1.4 (1.2–1.5)	1.5 (1.4–1.7)
Dairy (gram/day)	484 (312–653)	414 (245–618)	379 (231–581)	329 (209–249)	483 (298–687)	385 (217–629)	347 (206–580)	297 (183–473)	484 (137–646)	421 (254–616)	386 (242–582)	341 (220–501)
Meat (gram/day)	108 (72–138)	103 (64–134)	100 (61–131)	85 (52–123)	143 (109–172)	132 (100–168)	128 (100–168)	119 (86–158)	102 (64–128)	96 (57–123)	86 (54–118)	72 (46–107)
Alcohol (gram/day)	2 (0–10)	4 (1–15)	6 (1–16)	10 (3–19)	6 (1–22)	10 (3–24)	13 (4–26)	17 (9–28)	1 (0–6)	3 (0–12)	4 (1–13)	8 (2–15)
Health indicator												
Hypertensive, %	39	38	36	35	31	32	29	31	41	40	39	36
Diabetic, %	2	2	1	1	1	1	1	1	2	2	1	1
Cholesterol ratio[d], mean ± SD	3.9 ± 1.4	3.8 ± 1.5	3.8 ± 1.4	3.7 ± 1.4	4.7 ± 1.6	4.5 ± 1.8	4.5 ± 1.5	4.4 ± 1.6	3.8 ± 1.3	3.6 ± 1.3	3.5 ± 1.3	3.4 ± 1.2
Systolic blood pressure (mmHg), mean ± SD	125 ± 20	124 ± 19	124 ± 19	122 ± 18	123 ± 16	123 ± 15	122 ± 15	123 ± 15	125 ± 20	125 ± 20	124 ± 20	122 ± 19

Participants' baseline characteristics are calculated by mMDS category as percentages for categorical variables and as means (standard deviation) and medians (inter-quartile ranges) for continuous variables.
High educational level: higher vocational education or university to examination or university completed.
[a] Physically active according to Cambridge physical activity index.
[b] Unsaturated fatty acids = monounsaturated fatty acids + polyunsaturated fatty acids.
[c] Fat ratio: (monounsaturated fat + polyunsaturated fat)/saturated fat.
[d] Cholesterol ratio = total cholesterol/HDL-cholesterol.

Table 2 Hazard ratios of heart failure per 1-point increment and per category of the modified Mediterranean diet score (mMDS) in the EPIC-NL study.

	1-point increment	Category 1 (low)	Category 2	Category 3	Category 4 (high)	P-value for linear trend
mMDS range	0–9	0–3	4	5	6–9	
Men						
Subjects, N; person years	9316; 138,755	2588; 38,385	2162; 32,129	2110; 31,477	2456; 36,764	
Heart failure events, N (%)	144 (1.5)	53 (2.0)	34 (1.6)	32 (1.5)	25 (1.0)	
Multivariable model, HR (95% CI)	0.88 (0.79–0.98)	1 (ref)	0.79 (0.51 –1.21)	0.80 (0.51 –1.24)	0.53 (0.33 –0.86)	0.02
Women						
Subjects, N; person years	27,645; 410,364	8676; 128,943	6339; 94,147	6090; 90,487	6540; 96,787	
Heart failure events, N (%)	489 (1.8)	183 (2.1)	120 (1.9)	78 (1.3)	108 (1.7)	
Multivariable model, HR (95% CI)	0.98 (0.93–1.04)	1 (ref)	0.97 (0.77 –1.22)	0.74 (0.57 –0.97)	1.07 (0.83 –1.36)	0.76

CI, confidence interval; HR, hazard ratio.
Adjusted for age, education level, smoking status, total energy intake, physical activity.

The different findings between men and women may be partly explained by differences in type and ascertainment of HF. The prevalence of HF was higher among women, likely because of their higher age, and the higher prevalence (compared to men) therefore is not necessarily an indication of better HF ascertainment in women. Rather, HF may have been undiagnosed in women more often than men, because of differences in distributions of HF types between men and women. HFrEF is the most common type in men whereas HFpEF is the most common type among women [21], and particularly HFpEF can remain undiagnosed compared to HFrEF [22]. This may have resulted in HF cases in the group of non-cases, specifically in women, resulting in diluted associations. Moreover, HFpEF and HFrEF have different underlying etiologies that respond differently to therapeutic interventions [23], and therefore possibly also to dietary interventions. However, we should be careful to extrapolate differences found by sex to HF subtypes as both HF subtypes appear in both sexes and we were not able to stratify on HF subtype in our analyses. Future studies that are able to stratify by HF subtype are warranted to clarify this issue.

Beneficial effects of Mediterranean-style diets are often ascribed to unsaturated fatty acids (MUFA) from fish and olive oil [24]. In the process of HF development, the metabolism of the heart makes a switch from burning fatty acids to glucose [25]. A diet rich in MUFA, may prevent the heart from making this switch. Previous studies in animal models for HF have indeed showed that unsaturated fatty acids prevent the heart from hypertrophy [25]. However, consumption of fish and olive oil is rather low in our study population, and analyses with exclusion of fish and fat ratio from the mMDS did not confirm these groups to be essential components of the association with HF. An alternative explanation for the protective association could be a lower sodium consumption related with lower meat consumption and a healthier diet in general [26], impacting on blood pressure as important HF risk factor. Also, high anti-oxidant intake coinciding with high mMDS may have contributed to lower HF risk [27], since inflammation is triggered by oxidative stress, which is in most cases associated with the pathophysiology of cardiovascular disease [28]. However, we cannot exclude that a higher adherence to mMDS reflects a healthy lifestyle in general that we may not have been able to fully adjust for in this observational study.

Strengths for this study include its prospective design, long follow-up and the large sample size to investigate HF. Also, our study included both men and women, what allowed us to investigate the association of mMDS with HF in men and women separately within one cohort.

Limitations include that HF cases were detected from registers of hospital admissions and causes of death. Although this is a valid source for case ascertainment [29], it likely includes particularly more severe cases of HF. HF patients treated by the GP who have never been hospitalized for HF are not included, and our findings are thus specifically applicable to more severe HF cases. Second, HF is an aging disease and the middle-aged population may not have developed HF during follow-up time yet, what could have attenuated associations. Third, dietary intake was assessed at baseline with an FFQ. FFQs are known to be prone to measurement errors. Moreover, changes in dietary patterns during follow-up were not considered. Both aspects could have led to attenuation of the associations. Fourth, the mMDS is a predefined score to quantify adherence to a Mediterranean-style diet. The quantification is based on the median intakes of the study population and therefore our conclusions are applicable to relative adherence rather than absolute adherence to the Mediterranean diet. The consumption patterns of the Dutch population generally deviate on multiple aspects from typical Mediterranean diets, such as the rather low intakes of fish and high intakes of dairy products, even among participants that score relatively high on the mMDS. This should be taken into account when interpreting our findings, meaning that our findings reflect associations of adherence to a 'Mediterranean style dietary pattern' instead of a 'Mediterranean dietary pattern' with HF.

In conclusion, our results support the hypothesis that promoting a Mediterranean style diet may be beneficial for

preventing HF, particularly in men. In women, we did not find associations of mMDS with HF. The underlying reasons for the differences in findings between men and women need further study.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2020.08.003.

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