Association between Mediterranean and Nordic diet scores and changes in weight and waist circumference: influence of *FTO* and *TCF7L2* loci[1–3]

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ABSTRACT

Background: Several studies have shown that adherence to the Mediterranean Diet measured by using the Mediterranean diet score (MDS) is associated with lower obesity risk. The newly proposed Nordic Diet could hold similar beneficial effects. Because of the increasing focus on the interaction between diet and genetic predisposition to adiposity, studies should consider both diet and genetics.

Objective: We investigated whether *FTO* rs9939609 and *TCF7L2* rs7903146 modified the association between the MDS and Nordic diet score (NDS) and changes in weight (Δweight), waist circumference (ΔWC), and waist circumference adjusted for body mass index (BMI) (ΔWC_{BMI}).

Design: We conducted a case-cohort study with a median follow-up of 6.8 y that included 11,048 participants from 5 European countries; 5552 of these subjects were cases defined as individuals with the greatest degree of unexplained weight gain during follow-up. A randomly selected subcohort included 6548 participants, including 5496 noncases. Cases and noncases were compared in analyses by using logistic regression. Continuous traits (ie, Δweight, ΔWC, and ΔWC_{BMI}) were analyzed by using linear regression models in the random subcohort. Interactions were tested by including interaction terms in models.

Results: A higher MDS was significantly inversely associated with case status (OR: 0.98; 95% CI: 0.96, 1.00), ΔWC ($\beta = -0.010$ cm/y; 95% CI: −0.020, −0.001 cm/y), and ΔWC_{BMI} ($\beta = -0.008$; 95% CI: −0.015, −0.001) per 1-point increment but not Δweight ($P = 0.53$). The NDS was not significantly associated with any outcome. There was a borderline significant interaction between the MDS and *TCF7L2* rs7903146 on weight gain ($P = 0.05$), which suggested a beneficial effect of the MDS only in subjects who carried 1 or 2 risk alleles. *FTO* did not modify observed associations.

Conclusions: A high MDS is associated with a lower ΔWC and ΔWC_{BMI}, regardless of *FTO* and *TCF7L2* risk alleles. For Δweight, findings were less clear, but the effect may depend on the *TCF7L2* rs7903146 variant. The NDS was not associated with anthropometric changes during follow-up. *Am J Clin Nutr* 2014;100:1188–97.

INTRODUCTION

When the association between diet and obesity is examined, dietary patterns have received increasing attention over the past decades. It seems more likely that an entire dietary pattern has an effect in relation to obesity rather than the presence or absence of a single specific dietary component (1). Despite some inconsistency, existing observational and experimental studies have

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suggested a beneficial effect of the Mediterranean diet as assessed by using the Mediterranean diet score (MDS)[4] on obesity (2–11).

Recently, a Nordic diet score (NDS) was proposed that including rye bread, oat meal, root vegetables, cabbages, fish, shellfish, and apples and pears (12). This score is used to assess adherence to a healthy Nordic diet and has been shown to be associated with a decrease in body weight in Swedish (13) and Danish (14) intervention trials in at-risk populations and lower mortality in a population-based Danish cohort (12), which might be partly explained by a beneficial effect on body weight. However, obesity is caused by a complex interplay between both behavioral and genetic factors (15). This interplay encourages nutrigenetic research that examines the interaction between genes and nutrition. A lack of consideration of the genetic makeup in these studies could explain the conflicting results on the MDS and obesity. To date, *FTO* and *TCF7L2* genes have, in large-scale genome-wide association studies, been shown to be the most important susceptibility genes for obesity (16, 17) and diabetes (18), respectively. The *FTO* gene, which relates strongly to concurrent obesity, confers an increase in BMI (in kg/m^2) of 0.26–0.66 per risk allele (19). However, the gene has not been consistently associated with changes in body weight (20, 21). In contrast, *TCF7L2* does not seem to confer its effect on diabetes through an independent effect on BMI (22); on the contrary, it has been suggested to be associated with lower body weight (23). In some studies, *TCF7L2* has been shown to interact with diet in relation to weight loss (24–26). These findings suggest that the genetic variation in *FTO* and *TCF7L2* genes could modify the association between the MDS and NDS and anthropometric changes. For the MDS, interactions with *FTO* have been examined in relation to obesity in 2 previous studies that showed no interaction (27, 28). However, these studies were conducted in high cardiovascular disease risk subjects, which may have presented a different association than that in the general population. To our knowledge, no previous studies have investigated possible interactions between genetic susceptibility and the NDS. Therefore, the aim of the current study was to investigate whether *FTO* rs9939609 and *TCF7L2* rs7903146 modify the association between the MDS and NDS and changes in obesity-related traits in the Diet, Obesity and Genes study (15).

SUBJECTS AND METHODS

Study design and participants

We used data from 6 cohorts in 5 countries participating in the European Prospective Investigation into Cancer and Nutrition study (29) as follows: Denmark, Germany, Italy, Netherlands (Doetinchem and Amsterdam/Maastricht as 2 separate cohorts because of differences in data collection at follow-up), and the United Kingdom. All cohorts were population-based and included both men and women. Inclusion criteria were as follows: participants were <60 y old at baseline and <65 y old at follow-up; had an available blood sample and baseline information on diet, height, and weight; had follow-up information on weight; had stable smoking habits; had no previous diagnosis of cancer, cardiovascular disease, or diabetes at baseline or during follow-up; and had an average annual weight change ≤5 kg/y. The study was approved by local review boards of all participating institutions. Written informed consent has been obtained from all participants before joining the study.

Case and subcohort definitions

Cases were defined as participants who experienced the greatest degree of unexplained weight gain identified by using residuals from a regression model of annual weight change on baseline values of age, weight, height, smoking status, and follow-up time. Regression models were run separately for each country and stratified by sex. In all countries except Italy, 600 male and 600 female cases were selected. Because the Italian cohort consisted of a general population-based sample of women who were participating in a population-based breast cancer screening program, men were underrepresented (27%). To follow the sex distribution in the original cohort, 300 male and 900 female cases were selected here.

The subcohort sample consisted of a random sample of the total eligible cohort and was drawn so that the number of noncases in each center equaled the number of cases (n = 1200). This method resulted in some cases also being selected for the random subcohort. Therefore, in all centers except Denmark, where the overlap between cases and the subcohort was negligible (n = 79), oversampling of the random subcohort was performed. In the random subcohort, 7061 participants were included of whom 5928 were noncases. In total, 11,928 persons were included in the study. Of these subjects, 11,114 persons had DNA successfully extracted. We lacked information on nutritional or anthropometric variables of 66 participants, which left 11,048 subjects (5552 cases and 5496 noncases; 6548 in the random subcohort) in the final study population (**Figure 1**). Demographic, anthropometric, and dietary characteristics of cases, noncases, and the random subcohort are shown in **Table 1**.

DNA extraction and genotyping

Genomic DNA was extracted from buffy coats by using a salting-out method for all participants except UK samples, where whole-genome amplified DNA was used. In total, DNA from 11,114 participants (93%) was extracted. DNA extraction was done at KBioscience. Genomic and amplified DNA samples were quality checked, quantified, and normalized to ∼100 ng/mL and 2.0 μg before genotyping. The quality assessment showed a good yield.

High-throughput single-nucleotide polymorphism (SNP) genotyping was carried out by using the Illumina BeadStation Genotyping System at IntegraGen. Genotyping was considered successful if the following criteria were met: a sample call rate >95%, SNP call rate >95%, and duplicate discordance rate <3%. We used Fisher's exact test to evaluate the Hardy-Weinberg equilibrium for all SNPs for each country separately. If a statistically significant deviance from this equilibrium was shown ($P < 0.001$), the SNP was excluded for that particular country. For the 2 included SNPs, no such exclusions were necessary.

[4]Abbreviations used: FFQ, food-frequency questionnaire; MDS, Mediterranean diet score; NDS, Nordic diet score; SNP, single-nucleotide polymorphism; WC, waist circumference; WC_{BMI}, waist circumference adjusted for BMI; ΔWC, changes in waist circumference; ΔWC_{BMI}, changes in waist circumference adjusted for BMI; Δweight, changes in weight.

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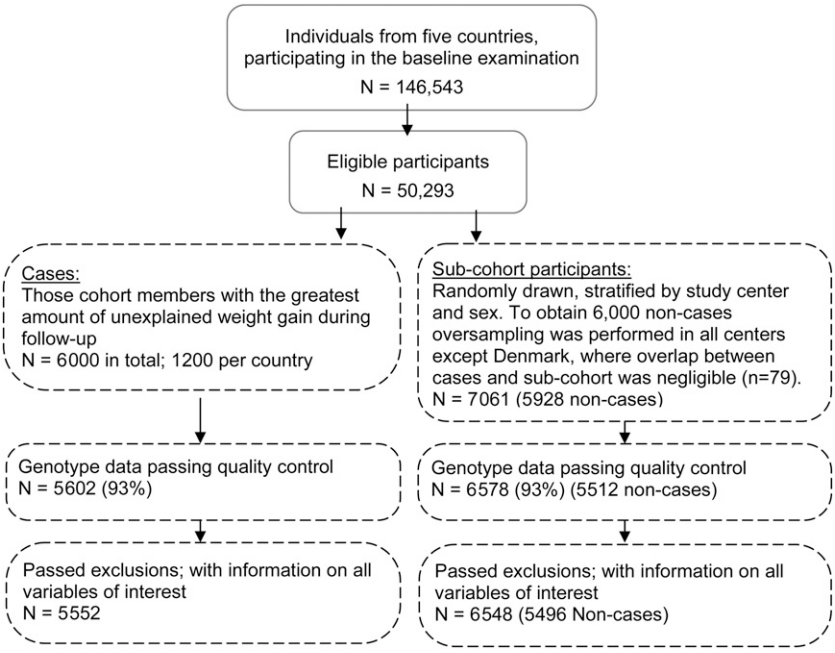

FIGURE 1. Flowchart of study participants.

SNP selection and linkage disequilibrium

We selected the following 2 genes for the current study: *FTO* and *TCF7L2*, on the basis of their consistent association in published, large-scale, genome-wide association studies with obesity and related traits (*FTO*) and risk of type 2 diabetes (*TCF7L2*) (16–18). For both genes, one SNP each was included as follows: rs9939609 (*FTO*) and rs7903146 (*TCF7L2*). Both SNPs are common variants with the following minor allele frequencies: A = 36% (rs9939609) and T = 22% (rs7903146) [dbSNP (www.ncbi.nlm.nih.gov/snp/) and HapMap (www.hapmap.org/) databases for individuals with European ancestry (CEU; HapMap Phase 3, Genome Build 37.3)].

Dietary data

Validated, country-specific food-frequency questionnaires (FFQs) were used to collect dietary information at baseline, including up to 260 items. In the Netherlands, Italy, and Germany, individual portion sizes were estimated, whereas in the United Kingdom and Denmark, standard portion sizes were assigned (29).

MDS

This study used the previously developed relative MDS (30), which includes 9 components characteristic of the Mediterranean diet. Some components were presumed to be beneficial (vegetables, legumes, fruit and nuts, cereals, fish and seafood, olive oil, and moderate alcohol consumption), and other components were presumed to be detrimental (meat, meat products, and dairy products). Each component (apart from alcohol) was measured in g per 1000 kilocalories (to express intake as energy density). All components (except olive oil and alcohol) were divided into sex-specific tertiles of intake on the basis of the original cohort. For beneficial components, values of 0, 1, and 2 were assigned to first, second, and third tertiles of intake, respectively. The scoring was reversed for the 2 detrimental components. The scoring for olive oil was modified because of the relatively large number of nonconsumers. In the current study, a value of zero was assigned to nonconsumers, a values of one was assigned to subjects with an intake below the median consumption (calculated within olive-oil consumers), and a values of 2 was assigned to subjects with intake at or above the median. For alcohol, a value of 2 was given to subjects with moderate consumption (women: 5–25 g/d; men 10–50 g/d), and a value of zero was assigned otherwise. The MDS ranges from 0 (minimal adherence) to 18 (maximal adherence). *See* Supplemental Figure 1 under "Supplemental data" in the online issue for the distribution.

NDS

The NDS used in the current study was originally developed and tested by Olsen et al (12). They defined it by including foods that were part of their FFQ, were originally grown in the Nordic countries, are commonly consumed in Nordic countries, and have health-beneficial effects (12). This method resulted in the inclusion of the following 6 food groups: whole-grain bread, oatmeal, apples and pears, cabbages, root vegetables, and fish and shellfish. For the current study, we did not have information on oatmeal, and therefore, the NDS consisted of the following 5 components: fish (all types of fish and fish contents in foods), cabbages (broccoli, white cabbage, Brussels sprouts, cauliflower, red cabbage, Savoy cabbage, green cabbage, sauerkraut, and Chinese cabbage), root vegetables (carrot, celery, beet root, turnip, parsnip, radish, and swede), apples and pears (apple, pear, compote of apple, and compote of pear), and dark bread (whole-grain bread, whole-meal bread, rye bread, brown bread, mixed-grain bread, whole-meal crisp bread, and bread sticks). These food items were chosen because of their status as traditional Nordic food items as well as their presumed health benefits. For each component, one point was given for intake above the sex-specific median of the total Diet, Obesity and Genes cohort. The NDS ranges from 0 (minimal adherence) to 5 (maximal

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TABLE 1
Distribution of anthropometric measures, dietary scores, and covariates in cases, noncases, and the random subcohort[1]

	Cases			Noncases			Random subcohort			
	All (n = 5552)	Men (n = 2492)	Women (n = 3060)	All (n = 5496)	Men (n = 2490)	Women (n = 3006)	All (n = 6548)	Men (n = 3013)	Women (n = 3535)	P-difference
Baseline age (y)	47.6 ± 7.5[2]	48.0 ± 7.4	47.3 ± 7.5	48.0 ± 7.3	48.4 ± 7.0	47.7 ± 7.5	47.9 ± 7.3	48.2 ± 7.2	47.7 ± 7.4	0.002
Baseline height (cm)	169.7 ± 9.4	177.1 ± 6.9	163.7 ± 6.4	169.4 ± 9.4	176.9 ± 6.8	163.3 ± 6.4	169.5 ± 9.5	176.9 ± 6.8	163.2 ± 6.4	0.15
Baseline weight (kg)	76.2 ± 14.3	83.8 ± 12.5	70.1 ± 12.6	72.6 ± 13.4	81.0 ± 11.1	65.7 ± 10.9	73.2 ± 13.6	81.4 ± 11.3	66.2 ± 11.1	<0.0001
Baseline BMI (kg/m^2)	26.4 ± 4.2	26.7 ± 3.7	26.2 ± 4.4	25.2 ± 3.6	25.9 ± 3.1	24.6 ± 3.9	25.4 ± 3.7	26.0 ± 3.2	24.8 ± 3.9	<0.0001
Baseline WC (cm)	87.5 ± 12.7	94.9 ± 10.5	81.6 ± 11.1	84.4 ± 12.0	92.5 ± 9.0	77.9 ± 9.9	84.9 ± 12.1	92.8 ± 9.3	78.3 ± 10.1	<0.0001
Baseline WC_{BMI}	0.2 ± 5.2	0.2 ± 4.8	0.2 ± 5.4	−0.2 ± 4.9	−0.2 ± 4.7	−0.2 ± 5.0	−0.1 ± 5.0	−0.2 ± 4.7	−0.1 ± 5.1	0.0002
ΔWeight (kg/y)	1.4 ± 0.7	1.4 ± 0.7	1.5 ± 0.7	0.03 ± 0.6	0.02 ± 0.6	0.04 ± 0.6	0.25 ± 0.8	0.24 ± 0.8	0.25 ± 0.8	<0.0001
ΔBMI (kg · m^{-2} · y^{-1})	0.5 ± 0.2	0.4 ± 0.2	0.6 ± 0.3	0.01 ± 0.2	0.01 ± 0.2	0.02 ± 0.2	0.09 ± 0.3	0.08 ± 0.2	0.09 ± 0.3	<0.0001
ΔWC (cm/y)	1.6 ± 1.2	1.4 ± 1.0	1.8 ± 1.3	0.51 ± 1.1	0.34 ± 1.0	0.64 ± 1.1	0.67 ± 1.1	0.52 ± 1.1	0.79 ± 1.2	<0.0001
ΔWC_{BMI} (cm/y)	0.02 ± 1.0	0.03 ± 1.0	0.01 ± 1.1	−0.03 ± 0.9	−0.05 ± 0.8	−0.02 ± 1.0	−0.02 ± 0.9	−0.03 ± 0.8	−0.02 ± 1.0	0.0042
MDS	8.8 ± 3.0	8.1 ± 2.9	9.3 ± 3.0	9.0 ± 3.0	8.3 ± 2.9	9.5 ± 3.0	9.0 ± 3.0	8.3 ± 2.9	9.6 ± 3.0	0.0003
NDS	2.3 ± 1.3	2.4 ± 1.2	2.3 ± 1.3	2.4 ± 1.3	2.4 ± 1.3	2.4 ± 1.3	2.4 ± 1.3	2.4 ± 1.3	2.3 ± 1.3	0.0126
Smoking status [n (%)]										<0.0001
Never	2404 (43.3)	892 (35.8)	1512 (49.4)	2592 (47.2)	992 (39.8)	1500 (53.2)	3035 (46.4)	1185 (39.3)	1850 (52.3)	
Former	1911 (34.4)	1052 (42.2)	859 (28.0)	1809 (32.9)	999 (40.1)	810 (27.0)	2190 (33.5)	1228 (40.8)	962 (27.2)	
Current	1237 (22.3)	548 (22.0)	689 (22.52)	1095 (19.9)	499 (20.0)	596 (19.8)	1323 (20.2)	600 (19.9)	723 (20.5)	
Education [n (%)]										<0.0001
None	13 (0.2)	2 (0.1)	11 (0.4)	3 (0.1)	0 (0)	3 (0.1)	4 (0.1)	1 (0.0)	3 (0.1)	
Primary school	1314 (23.7)	525 (21.1)	789 (25.8)	1081 (19.7)	439 (17.6)	642 (21.4)	1323 (20.2)	533 (17.7)	790 (22.4)	
Technical school	1930 (34.76)	852 (34.19)	1078 (35.23)	1860 (33.89)	832 (33.4)	1028 (34.2)	2219 (33.9)	1031 (34.2)	1188 (33.6)	
Secondary school	870 (15.7)	320 (12.8)	550 (18.0)	853 (15.5)	303 (12.2)	550 (18.3)	1038 (15.9)	371 (12.3)	667 (18.9)	
University	1259 (22.7)	707 (28.4)	552 (18.0)	1563 (28.4)	859 (34.9)	694 (23.1)	1792 (27.4)	1009 (33.5)	783 (22.2)	
Unknown	166 (3.0)	86 (3.5)	80 (2.6)	136 (2.5)	4 (1.9)	89 (3.0)	172 (2.6)	68 (2.3)	104 (2.9)	
Physical activity [n (%)]										0.006
Inactive	889 (16.0)	343 (13.8)	546 (17.8)	747 (13.6)	307 (12.3)	440 (14.6)	927 (14.2)	384 (12.7)	543 (15.4)	
Moderately inactive	1734 (31.2)	675 (27.7)	1059 (24.6)	1730 (31.5)	690 (27.7)	1040 (34.6)	2041 (31.2)	833 (27.7)	1208 (34.2)	
Moderately active	1300 (23.4)	618 (24.8)	682 (22.3)	1301 (23.7)	595 (23.9)	706 (23.5)	1534 (23.4)	716 (23.8)	818 (23.1)	
Active	1408 (25.4)	739 (29.7)	669 (21.9)	1452 (27.2)	798 (32.1)	694 (23.1)	1769 (27.0)	953 (31.6)	816 (23.1)	
Unknown	221 (4.0)	117 (4.7)	104 (3.4)	226 (4.1)	100 (4.0)	126 (4.2)	277 (4.2)	127 (4.2)	150 (4.2)	
Menopausal status [n (%)]										0.003
Premenopausal	1482 (26.7)	0 (0)	1482 (48.4)	1383 (25.1)	0 (0)	1383 (46.0)	1653 (25.24)	0 (0)	1653 (46.8)	
Postmenopausal	815 (14.7)	0 (0)	815 (26.6)	923 (16.8)	0 (0)	923 (30.7)	1059 (16.2)	0 (0)	1059 (30.0)	
Perimenopausal	671 (12.1)	0 (0)	671 (21.9)	637 (11.6)	0 (0)	637 (21.2)	748 (11.4)	0 (0)	748 (21.2)	
Surgical menopause	92 (1.7)	0 (0)	92 (3.0)	63 (1.2)	0 (0)	63 (2.1)	75 (1.2)	0 (0)	75 (2.1)	
NA/unknown	2492 (44.9)	2492 (100)	0 (0)	2490 (45.3)	2490 (100)	0 (0)	3013 (46.0)	3013 (100)	0 (0)	
Hormone use [n (%)]										0.907
No	2475 (44.6)	0 (0)	2475 (80.9)	2428 (44.2)	0 (0)	2428 (80.8)	2855 (43.6)	0 (0)	2855 (80.8)	
Yes	496 (8.9)	0 (0)	496 (16.2)	491 (8.9)	0 (0)	491 (16.3)	569 (8.7)	0 (0)	569 (16.1)	
NA/unknown	2581 (46.5)	2492 (100)	89 (2.9)	2577 (46.9)	2490 (100)	87 (2.9)	3124 (47.7)	3013 (100)	111 (3.1)	

[1] Cases were defined as 1200 participants from each cohort who experienced the greatest degree of unexplained weight gain over the study period and identified by using residuals from a regression model of annual weight change on baseline values of age, weight, height, smoking status, and follow-up time. P-difference values were calculated by using a 2-sample t test on all cases compared with noncases. MDS, Mediterranean diet score; NA, not answered; NDS, Nordic diet score; WC, waist circumference; WC_{BMI}, waist circumference adjusted for BMI; ΔBMI, changes in BMI; ΔWC, changes in waist circumference; ΔWC_{BMI}, changes in waist circumference adjusted for BMI; Δweight, changes in weight.

[2] Mean ± SD (all such values).

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adherence). *See* Supplemental Figure 1 under "Supplemental data" in the online issue for the distribution.

Covariates and outcome information

Participants filled in a questionnaire on demographics and lifestyle and health factors, including, among others, age, sex, physical activity [Cambridge Physical Activity Index (31)], education (none, primary school, technical school, secondary school, university, and unknown), smoking status (never, former, or current), and, for women, also hormone use (yes or no) and menopausal status (presurgical, perisurgical, or postsurgical). In addition, anthropometric measures were collected including height, weight, waist circumference (WC), and hip circumference. Participants were recontacted, on average, 6.8 y after enrollment to obtain information on changes in weight (Δweight), changes in waist circumference (ΔWC), and changes in lifestyle (29).

At baseline, participants were measured for weight, height, and WC. At follow-up, participants in Norfolk (United Kingdom) and Doetinchem (Netherlands) were measured by trained personnel, whereas remaining participants provided self-reported measures according to guidance. In the current study, investigated outcomes were annual Δweight, ΔWC, and changes in WC adjusted for BMI (ΔWC_{BMI}), which were defined as residuals of WC regressed on BMI (sex- and study-specific regressions; separately for baseline and follow-up values). This outcome was included to assess the association of changes in WC independent of changes in BMI. Changes were calculated as

$$\text{Follow-up values} - \text{baseline values} \div \text{follow-up duration} \quad (1)$$

Statistical methods

We examined the association of the MDS and NDS (exposures) with Δweight, ΔWC, and ΔWC_{BMI} (outcomes) in the random subcohort only by using linear regression analyses. The association with risk of being a weight gainer (case) was investigated by using logistic regression analyses for comparisons of cases with noncases. We examined whether associations differed for men and women by examining 2-factor interactions between diet scores and sex.

When the 2 SNPs were analyzed, participants were categorized according to the 3 genotypes for a SNP as follows: major allele homozygotes, heterozygotes, and minor allele homozygotes. All analyses assumed an additive effect of the minor allele (coded as 0, 1, or 2), which coincides with risk alleles of the *FTO* and *TCF7L2* SNPs for obesity and type 2 diabetes, respectively.

To examine whether genetic variants modified the association between diet scores and anthropometric outcomes, interactions were tested by including an interaction term (diet score × SNP) and also a SNP main effect term in the regression model including diet main effects. When a reference slope of the diet effect on outcome was considered, derived βs could be interpreted as estimated interaction effects (changes of slope) when increasing the diet score one unit and moving one step up in the number of risk alleles (from 0 to 1 and 1 to 2). We further tested whether interactions differed for men and women by examining 3-factor interactions of genes, diet, and sex.

All analyses were adjusted for sex, physical activity, education, and, for women, also hormone use and menopausal status. Random subcohort analyses were further adjusted for baseline age, height, and outcome measures (all continuous), follow-up time (continuous), and smoking status.

Analyses were initially conducted for each study cohort separately and subsequently meta-analyzed by using a random-effects model, which accounted for possible heterogeneity across study cohorts. Heterogeneity was tested by using Q statistics (32). Only pooled estimates from meta-analyses are presented in this article paper, whereas individual forest plots of meta-analyzed results can be seen in the supplementary material (*see* Supplemental Figures 2–7 under "Supplemental data" in the online issue). $P < 0.05$ was considered significant. Statistical analyses were conducted with Stata 11.2/12.1 software (StataCorp LP).

RESULTS

Main effects of SNPs on anthropometric measures

This article focuses on diet-score main effects and interaction analyses of SNP × diet scores in relation to anthropometric measures. Analyses of SNP main effects are only presented briefly because the main effect of rs9939609 has previously been investigated in this cohort (33). Analyses showed that the A allele was significantly associated with BMI [$\beta \pm$ SE = 0.17 ± 0.08 per allele ($P = 0.034$)] and WC [$\beta \pm$ SE = 0.47 ± 0.21 cm/allele ($P = 0.026$)] at baseline but not with weight change during follow-up [per allele: $\beta \pm$ SE = 5.55 ± 12.5 g/y ($P = 0.66$) in the random subcohort]. However, risk of being a weight gainer in the case-noncase analyses was increased (OR: 1.06; 95% CI: 1.00, 1.11; $P = 0.045$) (33). We analyzed the main effect of rs7903146 and showed no relation to any outcome (ΔWC: $\beta = -0.01$; 95% CI: −0.06, 0.04; $P = 0.72$; ΔWC_{BMI}: $\beta = 0.01$; 95% CI: −0.02, 0.04; $P = 0.62$); Δweight: $\beta = -0.03$; 95% CI: −0.07, 0.02; $P = 0.21$) or case status (OR = 0.92; 95% CI: 0.82, 1.03; $P = 0.13$).

Main effects of MDS and NDS on anthropometric measures

In the random subcohort, there was a significant association between the MDS and ΔWC ($P = 0.03$) and ΔWC_{BMI} ($P = 0.02$). Every point increase in the MDS was associated with a decrease in WC of −0.01 cm/y (95% CI: −0.02, −0.001 cm/y), and a decrease in WC_{BMI} of −0.008 cm/y (95% CI: −0.015, −0.001 cm/y). There was an inverse association between the MDS and risk of being a weight gainer (case) [OR: 0.98 (95% CI: 0.96, 1.00) per 1 point increment; $P = 0.04$]. The MDS was not associated with Δweight ($P = 0.53$).

Inverse associations were also observed for the NDS. Except for ΔWC_{BMI}, which were larger than for the MDS, effect sizes were of a similar magnitude. However, none of the associations were significant (all $P \geq 0.13$). There were no significant interactions with sex for either the MDS or NDS (**Table 2**).

Gene-diet interactions

There was a borderline significant interaction between the MDS and *TCF7L2* rs7903146 in relation to Δweight ($\beta = -0.02$; 95% CI: −0.03, 0.00; $P = 0.05$) (**Table 3**). We showed that, with a low MDS, there was very little difference in effect between genotypes, whereas at a higher MDS, participants with 1 or 2 minor alleles experienced a lower weight gain per year over the

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TABLE 2
Main effects of Mediterranean and Nordic diet scores on changes in anthropometric measure in the random subcohort and case-noncase analyses[1]

	Mediterranean diet score				Nordic diet score			
	P-heterogeneity across cohorts	Values	*P*	*P*-sex interaction	*P*-heterogeneity across cohorts	Values	*P*	*P*-sex interaction
Random subcohort analyses[2]								
ΔWC (cm/y)	0.50	−0.01 (−0.02, −0.001)	0.03	0.71	0.59	−0.008 (−0.03, 0.010)	0.42	0.24
ΔWC_{BMI} (cm/y)[3]	0.64	−0.008 (−0.015, −0.001)	0.02	0.54	0.71	−0.01 (−0.03, 0.003)	0.13	0.56
ΔWeight (kg/y)	0.86	−0.002 (−0.009, 0.005)	0.53	0.46	0.65	−0.006 (−0.02, 0.008)	0.40	0.99
Case-noncase analyses[4]								
Risk of being a weight gainer	0.17	0.98 (0.96, 1.00)	0.04	0.61	0.18	0.98 (0.93, 1.02)	0.23	0.38

[1] ΔWC, changes in waist circumference, ΔWC_{BMI}, changes in waist circumference adjusted for BMI; Δweight, changes in weight.
[2] All values are βs; 95% CIs in parentheses. Values were calculated by using linear regression models and adjusted for sex, physical activity (Cambridge Physical Activity Index), educational level, hormone use (women only), menopausal status (women only), baseline age (continuous), baseline height (continuous), baseline outcome measure (continuous), follow-up time (continuous), and smoking status (never, former, and current).
[3] Defined as sex- and study-specific residuals of waist circumference regressed on BMI.
[4] All values are ORs; 95% CIs in parentheses. Values were calculated by using logistic regression analysis for comparison of cases with noncases. Cases were defined as 1200 participants from each cohort who experienced the greatest degree of unexplained weight gain over the study period identified by using residuals from a regression model of annual weight change on baseline values of age, weight, height, smoking status, and follow-up time. Values were adjusted for sex, physical activity (Cambridge Physical Activity Index), educational level, hormone use (women only), and menopausal status (women only).

study period, which increased with the number of alleles, than for those homozygous for the major allele (C) (**Figure 2**). The regression-slope for each genotype-specific group was as follows: CC, 0.008, CT, −0.008; and TT, −0.024.

There were no significant interactions in relation to other outcomes or with *FTO* rs9939609. For the NDS, there were no significant interactions with the 2 included SNPs in relation to any of the outcomes (all $P \geq 0.21$).

We observed a significant 3-factor interaction between the *FTO*, NDS, and sex in relation to ΔWC_{BMI} ($P = 0.02$) (Table 3). In sex-specific analyses, there was an interaction between *FTO* and the NDS in women ($P = 0.015$) but not men ($P = 0.346$). For men, the genotype-specific regression-slopes were as follows: major allele homozygotes, −0.004; heterozygous, −0.017; and minor allele homozygous, −0.030. For women, the genotype-specific regression-slopes were opposing as follows: major allele

TABLE 3
Interactions between *FTO* rs9939609 and *TCF7L2* rs7903146 and Mediterranean and Nordic diet scores in relation to changes in anthropometric measures in random subcohort and case-noncase analyses[1]

		Mediterranean diet score			Nordic diet score		
	Risk allele	Values	*P*	*P*-sex interaction	Values	*P*	*P*-sex interaction
Random subcohort[2]							
ΔWC (cm/y)							
FTO rs9939609	A	−0.004 (−0.017, 0.010)	0.60[3]	0.99	0.0003 (−0.027, 0.028)	0.98[3]	0.31
TCF7L2 rs7903146	T	−0.015 (−0.033, 0.003)	0.11[3]	0.75	−0.006 (−0.051, 0.039)	0.80[3]	0.69
ΔWC_{BMI} (cm/y)[4]							
FTO rs9939609	A	0.002 (−0.008, 0.011)	0.73[3]	0.21	0.013 (−0.007, 0.033)	0.21[3]	0.02
TCF7L2 rs7903146	T	−0.003 (−0.017, 0.012)	0.70[3]	0.78	0.003 (−0.031, 0.036)	0.86[3]	0.88
ΔWeight (kg/y)							
FTO rs9939609	A	−0.004 (−0.014, 0.005)	0.41[3]	0.33	−0.001 (−0.029, 0.027)	0.94[3]	0.64
TCF7L2 rs7903146	T	−0.016 (−0.032, 0.000)	0.05[3]	0.50	−0.016 (−0.044, 0.011)	0.24[3]	0.79
Case-noncase analyses[5]							
FTO rs9939609	A	0.99 (0.96, 1.01)	0.22	0.92	0.98 (0.94, 1.03)	0.50	0.52
TCF7L2 rs7903146	T	0.99 (0.96, 1.01)	0.22	0.59	0.98 (0.93, 1.04)	0.51	0.77

[1] ΔWC, changes in waist circumference; ΔWC_{BMI}, changes in waist circumference adjusted for BMI; Δweight, changes in weight.
[2] All values are βs; 95% CIs in parentheses. Values were calculated by using linear regression models. βs for the interaction term were adjusted for sex, physical activity (Cambridge Physical Activity Index), educational level, hormone use (women only), menopausal status (women only), baseline age (continuous), baseline height (continuous), baseline outcome measure (continuous), follow-up time (continuous), and smoking status (never, former, and current).
[3] For gene × diet interaction.
[4] Defined as sex- and study-specific residuals of waist circumference regressed on BMI.
[5] All values are ORs; 95% CIs in parentheses. Values were calculated using logistic regression analysis for comparison of cases with noncases. Cases were defined as 1200 participants from each cohort who experienced the greatest degree of unexplained weight gain over the study period identified by using residuals from a regression model of annual weight change on baseline values of age, weight, height, smoking status, and follow-up time. ORs for unexplained weight gain were adjusted for sex, physical activity (Cambridge Physical Activity Index), educational level, hormone use (women only), and menopausal status (women only).

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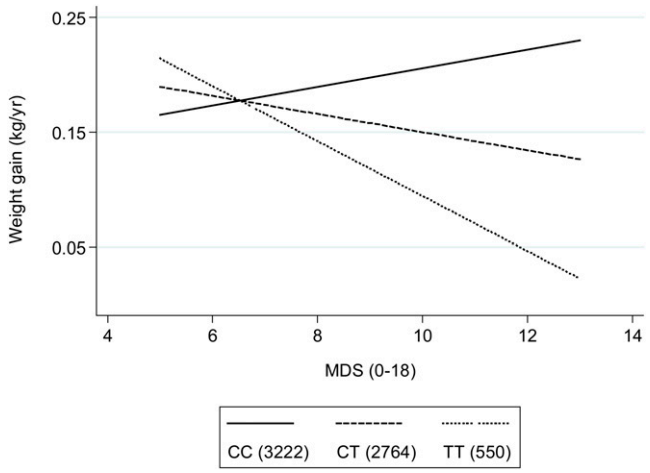

FIGURE 2. Interaction between the MDS and rs7903146 [major allele homozygous: CC (n = 3222); heterozygous: CT (n = 2764); and minor allele homozygous: TT (n = 550)] in the *TCF7L2* gene in relation to weight gain in random subcohort analyses (P = 0.05) calculated by using linear regression analysis. Regression slopes: CC, 0.008; CT, −0.008; and TT, −0.024. MDS, Mediterranean diet score.

homozygotes, −0.038; heterozygous, −0.004; and minor allele homozygous, 0.030, which suggested a beneficial effect of the NDS on ΔWC_{BMI} in major allele homozygotes (TT) only (**Figure 3**).

For both main effects and interaction analyses, no significant heterogeneity was shown between study cohorts (*see* Supplemental Figures 2–7 under "Supplemental data" in the online issue).

DISCUSSION

In this study of 11,048 individuals, we showed that a higher MDS was associated with a decrease in WC and WC_{BMI} as well as risk of being a weight gainer but not with weight change. A higher NDS score was not associated with changes in anthropometric measures during follow-up. The only borderline significant gene × diet interaction in this study was observed between the MDS and *TCF7L2* rs7903146 in relation to weight gain, which confined beneficial effects of a higher MDS to individuals with 1 or 2 rs7903146 risk alleles (T). The magnitude of effect of the MDS and NDS in relation to outcomes was similar for the 2 scores. However, associations were only significant for the MDS.

Few previous studies have investigated associations between the Nordic diet and anthropometric measures. In line with our results, an intervention study in 200 obese subjects did not find an effect of a diet that was based on Nordic Nutrition Recommendations (34) on body weight over an 18–24-wk period (P = 0.10) compared with a control diet that was based on mean nutrient intakes in Nordic countries (35). In contrast, a Swedish intervention trial that compared a habitual Western diet with a Nordic diet, showed a significant decrease in body weight in 88 mildly hypercholesterolemic subjects over 6 wk in adherers to the Nordic diet (−4%, $P < 0.01$) (13). Furthermore, a Danish intervention trial in 147 obese subjects that compared a New Nordic Diet (high in fruit, vegetables, whole grain, and fish) with an average Danish diet showed a significantly larger decrease in body weight, WC, and hip circumference (all $P \leq 0.03$) over 26 wk in the New Nordic Diet group (14). However, these were all intervention studies that targeted obese or otherwise abnormal subpopulations by using a specifically constructed diet with strict criteria for compliance. Thus, direct comparisons with our findings on the NDS are difficult because the NDS was constructed on the basis of the intake distribution in the population (by using sex-specific median intakes as cutoffs) and not by using predefined cutoffs.

The role of the MDS in relation to obesity has been examined more extensively, and despite some discrepancies, several reviews have suggested an inverse association with both the current anthropometric status and anthropometric changes in observational as well as experimental studies (2–6). These finding support our finding of an inverse association between the MDS and changes in overweight and obesity, albeit only for risk of being a weight gainer, ΔWC, and ΔWC_{BMI} but not Δweight. The finding of an association with risk of being a weight gainer but not Δweight seemed contradictory because cases were defined as subjects with the largest unexplained weight gain. However, the result may be explained by the fact that cases were defined

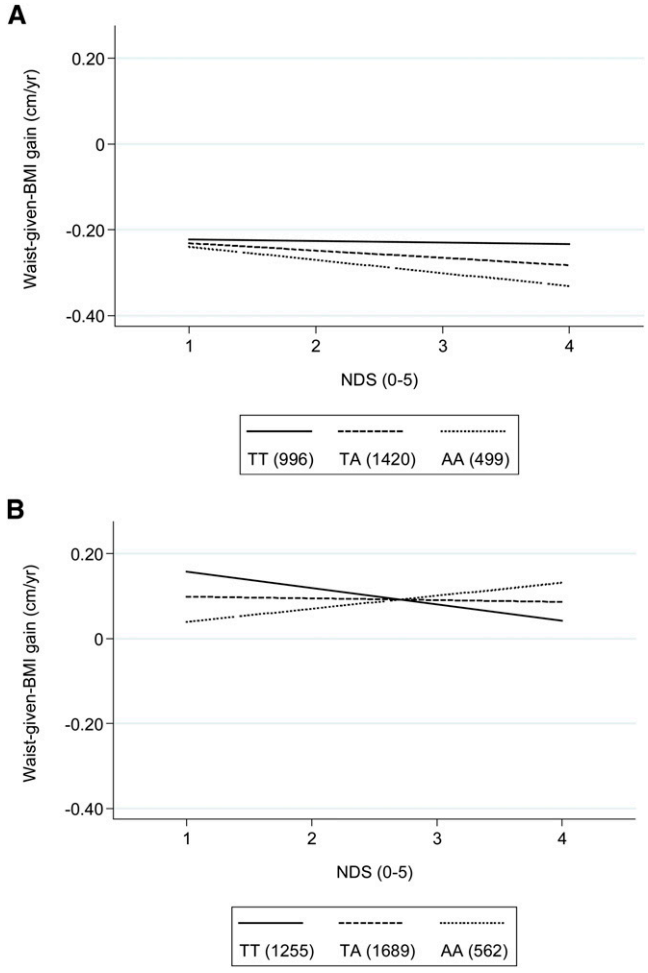

FIGURE 3. Interaction between the NDS and rs9939609 [major allele homozygous: TT (n = 996 men and 1255 women); heterozygous: TA (n = 1420 men and 1689 women); and minor allele homozygous: AA (n = 499 men and 562 women)] in the *FTO* gene in relation to changes in waist circumference adjusted for BMI in random subcohort analyses. Sex-specific results, P = 0.346 for men (A), P = 0.015 for women (B). All results were calculated by using linear regression analyses. NDS, Nordic diet score.

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as the most-extreme weight gainers. The rather small effect of the MDS may be overlooked when the whole spectrum of weight gain is considered and may only be visible in this extreme group.

A range of plausible biological mechanisms could explain the observed inverse association between the MDS and risk of being a weight gainer. The Mediterranean diet is high in dietary fiber, legumes, fruit, and vegetables, which may increase satiety and lower energy intake. The diet also has high contents of fish and olive oil, which are 2 sources of unsaturated fat that have been shown to entail losses of total weight and fat mass when they replaced saturated fat in intervention studies. Finally, a combined dietary profile with many plant-based foods and few meat and dairy products may lower the energy density of the diet (36). The Nordic dietary pattern has not been reviewed similarly in relation to obesity but several of the previously mentioned mechanisms may hold here as well because the Nordic dietary pattern is also characterized by high intakes of fish, dietary fiber, and plant-based foods (37). Also, several components of the NDS [ie, whole grain (38), cereal fiber (39), cabbage (40), and apples and pears (41, 42)] have individually been associated to lower risk of obesity. The lack of significant effects of the NDS in this study may have been be ascribed to the fact that the NDS contains fewer dietary items and, thus, may not capture a large enough proportion of and variation in participants' diets. The MDS uses a 19-point scale, and the NDS used a 6-point scale; this difference allows for a larger total gain by the MDS. Also, the MDS gives negative points for intakes of dairy and meat, whereas the NDS does not. This difference hampers the comparability of the 2 scales. A study in Swedish women showed that the NDS was positively associated with higher intakes of meat and total energy (Roswall et al, unpublished observations, 2014), which are factors that the NDS does not capture.

Two studies examined interactions between *FTO* rs939609 and the MDS in relation to obesity and anthropometric changes, and consistent with our results, they showed no interaction (27, 28). We have not identified any studies on interactions between *TCF7L2* rs7903146 and the MDS in relation to anthropometric measures. However, one study showed an interaction in relation to cardiovascular disease risk factors, whereby, when the MDS was low, TT homozygotes had higher fasting glucose concentrations than those for CC or CT genotypes, whereas this difference disappeared when the MDS was high. A similar interaction was observed in relation to LDL and total cholesterol, triglycerides, and stroke risk (43). In parallel, the current study suggested a beneficial effect of the MDS in individuals with 1 or 2 risk alleles only (Figure 2). To our knowledge, none of the existing studies on the NDS and obesity included genetic information. This lack encourages the reproduction of our findings.

In this article, we, to a large extent, focused on gene-diet interactions. Such interactions may be seen and interpreted in 2 distinct ways as to which extent the genetic information affects the dietary effect or, reversely, to which extent dietary intake affects the genetic effect. Explicitly, for standard linear regressions, interactions are here fitted as linear interaction effects related to the selected actual respective continuous outcomes and, for logistic regressions (case-noncase analyses), as linear interaction effects on the log-OR scale (and, hence, as corresponding multiplicative effects on the OR scale). In all cases, a strong interaction effect would indicate that it is not enough to consider separate factors independently with respect to, eg, predictions, but also their joint interactive effects are important in this sense.

The strengths of this study included the use of a random-effects model meta-analysis across the included cohorts. The prospective design eliminated risk of a recall bias, and the comprehensive and valid follow-up minimized risk of a selective dropout. All participants provided comprehensive information on diet and potential confounders, allowing for control for these. Because of the standardized and validated FFQs, we could directly compare and combine findings across study centers (29). The inclusion of populations from several countries allowed for the examination of dietary scores and their interactions with genetics in different settings with more or less adherence. The exclusion of persons with type 2 diabetes should have eliminated an ascertainment bias of the association between *TCF7L2* and obesity traits.

The FFQ has been validated in a representative sample of participants (44–46). The collection of one dietary assessment only used as a proxy for the entire period may have been a limitation because changes in dietary habits could have occurred during follow-up. This use may have diluted the effects and, hence, weakened associations. Also, the 2 diet scores only partially captured the entire diet, and, especially for the NDS, this corresponds to a rather small, although presumably quite important, proportion. With the use of a composite dietary index, the magnitude of measurement error may increase; however, most likely, the error will be unsystematic, affecting estimates toward unity. An information bias may have existed for included confounders, which could have induced residual confounding, but the validity of physical activity has been evaluated with positive results (31, 47). Anthropometric measures at follow-up were self-reported in 4 of 6 study centers, which may have induced a misclassification. However, we did not observe heterogeneity between centers that used self-reported and measured data. Furthermore, a previous study showed that correcting self-reported information by methods developed for the European Prospective Investigation into Cancer and Nutrition study (48) did not significantly change results (49).

In conclusion, the current study shows a small but significant inverse association between the MDS and changes in WC, WC_{BMI}, and extreme weight gain, but not weight gain in general, over 6.8 y follow-up. There was a similar tendency toward an inverse association for the NDS, but this was not significant. The only gene $\times$ diet interaction shown was a borderline significant interaction between the MDS and *TCF7L2* rs7903146 on weight gain over the study period, which confined beneficial effects of a high MDS to individuals with 1 or 2 rs7903146 risk alleles. The replication of our findings in another cohort is recommended.

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The authors' responsibilities were as follows—NR, AT, and TIAS: conceived the current study; NR, DR, TIAS, NJW, DP, DLvdA, HB, and RJFL: designed the research; NR, LÄ, and DR: conducted the research; KSV, RJFL, AT, NJW, DP, DLvdA, and HB: provided essential material; LÄ: analyzed data; NR, LÄ, TSA, SCL, JNØ, JH, KSV, BB, JMAB, and RJFL: wrote the manuscript; TIAS and AT: had primary responsibility for the final content of the manuscript. None of the authors had a conflict of interest.

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