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Relationship Of Mediterranean Diet And Caloric Intake To Phenoconversion In Huntington Disease

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Abstract

Importance—Adherence to Mediterranean-type diet (MeDi) may delay onset of Alzheimer's and Parkinson's disease. Whether adherence to MeDi affects time to phenoconversion in Huntington's Disease (HD), a highly penetrant, single gene disorder, is unknown.

Objective—To determine if MeDi modifies the time to clinical onset of HD ('phenoconversion') in premanifest carriers participating in Prospective Huntington At Risk Observational Study (PHAROS), and to examine the effects of BMI and caloric intake on time to phenoconversion.

Design—A prospective cohort study.

Setting—41 Huntington Study Group sites in the US and Canada.

Participants—1001 participants were enrolled in PHAROS between July 1999 and January 2004, and were followed every 9 months until 2010. A total of 211 participants aged 26–57 with an expanded CAG repeat (≥37) were included in the current study.

Exposure—A semi-quantitative food frequency questionnaire (FFQ) was administered 33 months after baseline. We calculated daily gram intake for dairy, meat, fruit, vegetables, legumes, cereals, fish, monounsaturated and saturated fatty-acids, and alcohol, and constructed MeDi scores (0–9); higher scores indicate higher adherence. Demographics, medical history, BMI, and Unified Huntington's Disease Rating Scale (UHDRS) were collected.

Main Outcome Measure—Cox proportional hazards models to determine the association of MeDi and phenoconversion.

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Results—Age, caloric intake, gender, education, and UHDRS motor scores did not differ among

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MeDi components calculated by Dr. Gu. Statistical analyses performed by Dr. Oakes and Ms. Eberly.

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MeDi tertiles (0–3, 4–5, 6–9). The highest BMI was associated with lowest adherence to MeDi. 31 participants phenoconverted. In a model adjusted for age, CAG, and caloric intake, MeDi was not associated with phenoconversion (p for trend=0.14 for tertile of MeDi, and p=0.22 for continuous MeDi). When individual diet components of MeDi were analyzed, higher dairy consumption (hazard ratio 2.36; 1.0–5.57; p=0.051) and higher caloric intake (p=0.035) were associated with risk of phenoconversion.

Conclusion and Relevance—MeDi was not associated with phenoconversion, however higher consumption of dairy products had a two-fold increased risk, and may be a surrogate for lower urate levels (associated with faster progression in manifest HD). Studies of diet and energy expenditure in premanifest HD may provide data for interventions to modify specific components of diet that may delay the onset of HD.

Keywords

Huntington disease; nutritional; cohort

Introduction

CAG repeat length is the primary determinant of age of onset of Huntington's disease (HD), but environmental modifiers of age of onset may also act. Converging evidence from both murine and human HD point to a procatabolic state that may antedate overt motor manifestations of HD.[1–3] Numerous studies have demonstrated that individuals with manifest HD have lower body mass index (BMI) than age-matched controls.[4–8] Weight loss is more prominent in humans and mice with greater CAG repeat length[9] and increases with disease progression.[4,6]

In a previous study,[10] we examined the relationship between BMI, diet, and HD onset by administering a semi-quantitative food frequency questionnaire (FFQ)[11,12] to participants in the Prospective Huntington At Risk Observational Study (PHAROS),[13] who were at risk for HD but had not undergone genetic testing at the time of enrollment. Since these participants did not know their genetic status, they were unlikely to have altered their diets differentially. We found no major differences in macronutrient consumption (protein, carbohydrates, fat) between expanded and non-expanded CAG repeat groups.

Humans eat meals with complex combinations of nutrients or food items that are likely to be synergistic (or antagonistic), so that the action of the food matrix is different in each individual. One particular dietary pattern, Mediterranean-like diet (MeDi), has been widely explored in relation to various neurological disorders[14,15]. MeDi, a diet high in plant foods (such as fruits, nuts, legumes, and cereals) and fish, with olive oil as the primary source of monounsaturated fat (MUFA) and low to moderate intake of wine, as well as low intake of red meat, poultry and dairy products, is known to be beneficial for health due to its protective effects in many chronic diseases.[16,17] Studies have found that higher adherence to a MeDi may delay the onset of Alzheimer's disease,[14] and may be associated with later age at onset of Parkinson's disease.[15] Nutritional supplements including Coenzyme Q10, Ethyl EPA, and creatine have been used in therapeutic trials in HD targeted at improving

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bioenergetics in manifest HD.[18] Double-blind placebo-controlled trials of specific dietary interventions have not been conducted in premanifest HD.

Our goals in this prospective study are 1) to determine whether adherence to a MeDi affects time to diagnosis of HD (phenoconversion) among participants in PHAROS and 2) to examine the effects of BMI and caloric intake on time to phenoconversion.

Subjects

All participants were enrolled in PHAROS between July 1999 and January 2004.[13] Institutional review boards at all participating sites approved the protocols and consent procedures. At baseline, participants were between 26 and 57 years of age, and at risk for HD by virtue of having an affected parent or sibling. At the time of enrollment, participants had not undergone genetic testing for the CAGn expansion. Blinded genetic testing was performed at the baseline visit, and investigators and participants remained blinded to gene status for the duration of the trial. Details of the baseline assessment of these 1001 individuals and blinding procedures have been published.[13] At each assessment, an independent rater at each site performed the motor component of the UHDRS and assigned a level of diagnostic confidence of HD based solely on this motor exam. A rating of 4 indicated ≥99% confidence of clinically definite HD based on the presence of an unequivocal otherwise unexplained extrapyramidal movement disorder.[19] The first time a rating of 4 was given was considered motor ‘phenoconversion’. Only participants who had an expanded CAG repeat (≥ 37) and who did not have a diagnostic confidence rating of 4 at enrollment were included in these analyses. Subjects who phenoconverted at the visit when the FFQ was completed, or for whom the visit was the last visit (n=15), were excluded since we were interested in phenoconversion.

Dietary Assessment

Seven hundred thirty-eight individuals completed at least one National Cancer Institute (NCI) FFQ, which has been shown to be reliable and valid.[12] The initial FFQ was administered, on average, 33 months after baseline examination. Details of the dietary assessment have been previously reported.[10] The analysis cohort includes 211 subjects with an expanded CAG repeat. A MeDi is defined by high consumption of vegetables, legumes, fruit and cereals, high intake of MUFA compared to saturated fatty acids (SFA), high intake of fish, low intake of meat (including poultry) and dairy products, and moderate consumption of alcohol (wine).

We followed the most commonly described method[16] to construct the MeDi score as described in our previous reports[14,20,21] http://onlinelibrary.wiley.com/doi/10.1002/ana.20854/full - bib31. More specifically, we first regressed total daily energy intake (measured in kilocalories) and calculated the derived residuals of daily gram intake[22] for each of the following seven categories: dairy, meat, fruits, vegetables, legumes, cereals, and fish. Individuals were assigned a value of 1 for each component presumed to be beneficial (fruits, vegetables, legumes, cereals, and fish) if his/her caloric-adjusted consumption was at or above the sex-specific median, and for each detrimental component (meat and dairy

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products) if the caloric-adjusted consumption was below the sex-specific median. Individuals were assigned a value of 0 for each beneficial component if the caloric-adjusted consumption was below the sex-specific median, and for each detrimental, at or above the sex-specific median. For the fat component, we used the ratio of daily consumption (in grams) of MUFA to SFA, and a value of 1 was assigned if the intake was at or above the sex-specific median, and 0 if below the sex-specific median. Finally, subjects were assigned a score of 0 for either <4 gm/day (approximately 1 glass of wine weekly) or more than moderate (≥30gm/day, approximately 1 glass of wine daily) consumption, and a value of 1 for mild-moderate alcohol consumption (≥4 to <30gm/day). The MeDi score was generated for each participant by adding the scores in the food categories, with a higher score indicating better adherence to the MeDi. Thus, the MeDi score theoretically ranges from 0–9, with 0 indicating the least adherence to the MeDi and 9 the strictest adherence to the MeDi.

Statistical Analyses

The “baseline” was considered to be the visit at which the FFQ was completed, and the MeDi score from that visit was used as the main predictor in the analyses. The MeDi score was analyzed as a continuous variable and then as tertiles (0–3, 4–5 and 6–9). The association between demographic and clinical variables and adherence to the MeDi was compared among MeDi tertiles. Cox proportional hazards models were used to determine whether adherence to the MeDi modified time to phenoconversion, adjusting for demographic and clinical variables in a fully adjusted model and in a second, smaller model including only significant covariates. Covariates in the full model included the following measures at the time of completion of the FFQ: age, body mass index (BMI), caloric intake, gender, education, Unified Huntington Disease Rating Scale (UHDRS) motor score, and the chorea subscore of the UHDRS. Lastly, nine individual components of the MeDi diet were included simultaneously in a model to predict phenoconversion, adjusting for age, CAG and caloric intake.

Results

Age, caloric intake, gender, education, Unified Huntington Disease Rating Scale motor score, and the chorea subscore did not differ among the MeDi tertiles (Table 1). The highest BMI was associated with the lowest adherence to MeDi (p=0.02), before adjustment for covariates. Thirty-one of the 211 subjects phenoconverted during the study period. Average time to phenoconversion was 2.5 (1.7) years for phenoconverters, compared to 4.3 (1.7) years of follow up for those who did not phenoconvert and were either followed until the end of the study or lost to followup. Not surprisingly, phenoconverters were significantly older (47.9 (5.5) years compared to 42.6 (7.7) years) and had slightly higher CAG repeat length (42.4 (1.4) compared to 41.7 (2)) than subjects who did not phenoconvert during the study period. In a fully adjusted model (Table 2), age and CAG repeat length were associated with phenoconversion, but adherence to MeDi was not. There was a trend for higher caloric intake, but not BMI, as a risk factor for phenoconversion. In a model including only significant covariates (age, CAG repeat length, caloric intake) MeDi was not associated with phenoconversion (p=0.14) and p=0.22 for continuous MeDi, but higher

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caloric intake was marginally associated (p for trend 0.0467) (Table 2). When individual components of the MeDi were analyzed, only higher consumption of dairy products was associated with an increased risk of phenoconversion, HR 2.36 (1.0–5.57) p=0.051 (Table 3); higher caloric intake was also associated with increased risk of phenoconversion in this model (p=0.0351).

Discussion

In some observational studies, adherence to the MeDi has been has been associated with reduced risk of certain neurological conditions and diseases including mild cognitive impairment[23], Alzheimer disease[14], cerebrovascular disease,[24,25] essential tremor[26] and Parkinson's disease[15]. Potential mechanisms for some of these disease modifying effects include an increased antioxidant effect[27] and reduced inflammation.[28] In this prospective study, we have shown that in individuals with an expanded CAG repeat (CAG≥ 37), higher BMI is associated with lower adherence to the MeDi, and higher caloric intake was marginally associated with risk for phenoconversion.

Higher consumption of dairy products was associated with a two-fold risk of phenoconversion after adjustment for age, CAG repeat length and caloric intake, echoing a retrospective study of 51 HD families in the Netherlands, in which higher milk consumption was associated with earlier onset of HD.[29] Numerous studies have shown an inverse relationship between consumption of dairy products and plasma uric acid, such that lower dairy consumption is associated with higher acute and long-term urate levels.[30] Higher urate levels have been associated with slower HD progression as measured by the total functional capacity scale over a 30 month period.[31] Urate levels have not been measured in premanifest HD [but have been measured in manifest HD]. Prospective studies[32–34] have demonstrated an increased risk of Parkinson's disease (PD) for the highest quartiles of dairy intake that could not be attributed to calcium intake, particularly in men. Possible explanations for this association include the presence of low levels of pesticides in milk, or the fact that higher dairy consumption is related to lower circulating levels of urate and lower risk of gout. Dairy alone is dose-dependently linked to PD risk, and the dietary urate index, linked to PD risk, is driven by the dairy product/protein ratio.[35] In this study, high dairy consumption may be a surrogate marker for low urate. High urate may slow progression of established HD and PD, and can lower PD risk. By extension, the two-fold increased risk of phenoconversion associated with dairy consumption could be associated with reduced urate levels.

Dietary interventions in HD have been examined on a small scale. A hypercatabolic profile was identified in both early HD and premanifest HD, characterized by low levels of branched chain amino acids. A trial of dietary triheptanoin to improve peripheral energy metabolism[18,36] using an anapleurotic approach was well tolerated, and a clinical trial is being planned. In a study of Wistar rats, extra virgin olive oil in conjunction with hydroxytyrosol was effective in reversing the effect of 3NP on succinate dehydroxenase, suggesting that a component of the MeDi was effective in reducing lipid peroxidation in an HD-like model.[37]

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We have previously shown that higher total caloric intake, but not BMI, was associated with a two-fold odds of carrying an expanded CAG repeat (≥ 37) after adjustment for total motor score on the Unified Huntington Disease Rating Scale (UHDRS) in the PHAROS cohort.[10] In the expanded group, higher caloric intake, but not BMI, was correlated with higher CAG (p=0.03) and increased the 5-year estimated probability of HD[38,39] (p=0.013). We concluded that increased caloric intake was necessary to maintain BMI in the premanifest state, but could not determine whether this was due to a hypermetabolic state, subtle involuntary movements, swallowing impairment or malabsorption. In this study we show that higher caloric intake, and not BMI, was marginally associated with risk for actual, rather than estimated phenoconversion.

Strengths of this study include the fact that participants did not know whether they carried an expanded CAG repeat and therefore did not differentially modify their diets. Because they did not have HD at the time of administration of the FFQ, caloric intake or BMI were unlikely to be affected by extrapyramidal signs. All participants were evaluated annually by movement disorders specialists who were also blind to genetic status. A validated FFQ and standard methods for caloric intake MeDi calculation and BMI measurements were used. The analyses were adjusted for several potential covariates. Limitations of the study include the administration of the diet survey at more than 30 months after study initiation, at which time there were individuals who had already developed HD or dropped out of the study, reducing our sample size and potentially introducing a survivorship bias.[10] Post hoc power calculations suggest that the study had 50% – 85% power to detect a hazard ratios in the range of 2.0 – 3.0, so that some moderate-sized associations may not have been detected. Dietary assessments were self-reports, and there was no opportunity to validate dietary intake. We cannot determine whether presymptomatic HD carriers of an expanded CAG repeat change their dietary preference as they approach phenoconversion. Exploration of individual food groups was in the form of dichotomous variables, while continuous scores could have provided additional power. Blood was collected only for DNA, so urate, calcium and other potential covariates cannot be examined.

The fact that in a highly penetrant single gene disorder, there could be risk factors that modify disease onset is promising. Our results, in the largest systematically followed at risk cohort at risk for HD, suggest that studies of diet and energy expenditure in premanifest HD may provide data for both non-pharmacological interventions or pharmacological interventions to modify specific components of diet, that may delay the onset of HD.

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Table 1

Characteristics of Participants with CAG≥37 (n=211) at FFQ Completion Date by MeDi Tertiles

	MeDi 0–3 N = 67	**MeDi 4–5 N = 94**	**MeDi 6–9 N = 50**	**P-Value**
Age	44.1 (35.9, 48.6)	44.0 (37.9, 48.6)	42.8 (36.3, 51.2)	0.66
CAG	42 (40, 43)	41.5 (40, 43)	42.5 (41, 44)	0.048
Caloric Intake	1847 (1376, 2176)	1764 (1414, 2306)	1785 (1480, 2597)	0.68
BMI	27.1 (23.4, 31.6)	26.2 (23.6, 29.6)	25.8 (22.1, 28.8)	0.025
UHDRS Motor	4 (1, 10)	3 (0, 8)	2 (1, 6)	0.10
Chorea	0 (0, 3)	0 (0, 2)	0 (0, 2)	0.59
Education	14 (13, 16)	16 (12, 17)	16 (14, 17)	0.09
Female Gender	51 (76%)	69 (73%)	32 (64%)	0.16

Values shown are median (25^{th} percentile, 75^{th} percentile) or N (%), as appropriate.

P-values shown are from trend tests from separate multiple regressions using ranks or from a Cochran-Armitage trend test, as appropriate.

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Table 2

Adjusted Hazard Ratios (HR) from Models to Predict Phenoconversion

	Full Model HR (95% CI)	P-Value	Small Model HR (95% CI)	P-Value
Age	1.14 (1.07, 1.22)	<0.0001	1.17 (1.10, 1.24)	<0.0001
Gender				
Male	1.0	0.31	--	--
Female	1.78 (0.58, 5.42)			
CAG	1.46 (1.10, 1.94)	0.0098	1.69 (1.32, 2.17)	<0.0001
Caloric Intake		0.07*		0.0467*
Low	1.0		1.0	
Medium	0.61 (0.19, 1.99)		0.97 (0.33, 2.85)	
High	1.70 (0.65, 4.43)		2.42 (0.99, 5.92)	
BMI				
Low	1.0	0.63*	--	--
Medium	0.47 (0.16, 1.36)			
High	1.41 (0.54, 3.64)			
UHDRS Motor				
<= 1	1.0	0.08	--	--
> 1	3.42 (0.84, 13.87)			
Chorea				
= 0	1.0	0.42	--	--
> 0	1.51 (0.56, 4.10)			
Education	1.11 (0.94, 1.30)	0.21	--	--
MeDi Diet		0.73*		0.14*
0 – 3	1.0		1.0	
4 – 5	1.03 (0.41, 2.57)		0.73 (0.32, 1.71)	
6 – 9	0.74 (0.23,2.42)		0.44 (0.15, 1.29)	

Hazard ratios and p-values shown are from Cox proportional hazards models (full model and small model) for time to phenoconversion.

*Trend test.

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Table 3

Association Between Individual MeDi Components and Phenoconversion

	Small Model HR (95% CI)	P-Value
Age	1.17 (1.10, 1.25)	<0.0001
CAG	1.68 (1.29, 2.19)	0.0001
Caloric Intake		0.0351*
Low	1.0	
Medium	0.87 (0.28, 2.75)	
High	2.69 (1.01, 7.15)	
Cereal (Low Intake)	1.12 (0.50, 2.48)	0.79
Dairy (High Intake)	2.36 (1.00, 5.57)	0.0507
Fish (Low Intake)	0.71 (0.29, 1.75)	0.46
Fruit (Low Intake)	0.74 (0.30, 1.82)	0.51
Legumes (Low Intake)	1.87 (0.75, 4.62)	0.18
Meat (High Intake)	0.86 (0.37, 1.98)	0.72
Vegetables (Low Intake)	2.05 (0.74, 5.72)	0.17
MUFA/SFA (Low Intake)	1.40 (0.61, 3.19)	0.43
Alcohol (Moderate Intake)	0.81 (0.36, 1.83)	0.61

Hazard ratios and p-values shown are from a single Cox proportional hazards model for time to phenoconversion.

* Trend test.

Lower than sex-specific median intake of detrimental components (i.e., dairy and meat) and higher than sex-specific median intake of beneficial components (i.e., cereal, fish, fruit, legumes, vegetables, MUFA/SFA, moderate alcohol) were treated as reference group.