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**Overall Diet History and Reversibility of the Metabolic Syndrome Over 5 Years:
The Whitehall II Prospective Cohort Study**

Running Title: Overall Diet and Reversion of Metabolic Syndrome

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ABSTRACT

Objective: We examined the impact of adherence to the [Alternative Healthy Eating Index \(AHEI\)](#), a set of dietary guidelines targeting major chronic diseases, on metabolic syndrome (MetS) reversion in a middle-aged population.

Research Design and Methods: Analyses were carried on the 339 participants (28% women, mean age 56.4 years) from the Whitehall II study with MetS defined by the National Cholesterol Education Program Adult treatment Panel III criteria. Reversion was defined as not having MetS after 5-years of follow-up (158 cases).

Results: After controlling for potential confounders, adherence to AHEI was associated with MetS reversion (odds ratio 1.88, 95% CI:1.04-3.41), predominantly in participants with central obesity and in those with high triglyceride.

Conclusions: Our findings support the benefit of adherence to AHEI dietary guidelines for individuals with MetS, especially those with central obesity or high triglyceride levels.

Keyword: Metabolic syndrome, Prospective study, the Alternative Healthy Eating Index

The metabolic syndrome (MetS), prevalence estimated at between 10% and 25% in adult populations worldwide[1], is associated with an increased risk of type 2 diabetes (T2D) and cardiovascular diseases (CVD). Lifestyle modification, such as increased physical exercise[2] and diet therapies[3, 4], may have a beneficial impact on MetS. We examined a set of dietary guidelines targeting major chronic diseases known as the Alternative Healthy Eating Index (AHEI)[5]. Our goal was to examine whether adherence to AHEI was associated with reversion of the MetS over a 5-year period in a middle-aged population.

RESEARCH DESIGN AND METHODS

Data came from phases 3 (1991-1993), 5 (1997-1999) and 7 (2002-2004) of the Whitehall II study of London based office workers[6]. From the 3698 participants with complete data on MetS at phases 3 and 5; diet and covariates at phase 5, and the outcome (MetS status at phase 7), the 339 MetS cases at phase 5 formed the study population for the main analysis.

At each phase, MetS was defined using the National Cholesterol Education Program Adult treatment Panel III criteria[7]. The definition of each MetS component plus details of other measurements are given in the footnote of Table 1 and have been described previously[8]. The 5-year reversion of MetS was defined as not having MetS at phase 7.

Dietary intake data were collected via a validated 127-item food frequency questionnaire (FFQ)[9-10] both at phases 3 and 5. AHEI score[5] was created by summing its 9 component scores (1/fruit, 2/vegetable, 3/ratio of white to red meat,

4/*trans* fat, 5/ratio of polyunsaturated to saturated fat, 6/total fiber, 7/nuts and soy, 8/alcohol consumption and 9/long-term multivitamin use); a higher score corresponded to greater adherence (Appendix-Table A1). We used the AHEI measures in two ways: the Phase 5 score for the main analysis and the average AHEI score across phases 3 and 5, to take into account longer-term adherence to AHEI, in subsidiary analysis on the 337 participants with complete dietary data from phases 3 and 5. Levels of AHEI adherence at phase 5 were comparable to those reported in two large American cohorts[5] (Appendix-Table A2).

Logistic regression models examined the association between tertiles of the AHEI scores at phase 5 and reversion of MetS and of its components at phase 7, sequentially adjusted for age, sex, ethnicity (White/non-White) and total energy intake (kcal/day) (Model 1) and for educational attainment (no academic qualification/lower secondary/higher secondary/university degree/higher university degree), marital status (married or cohabiting/living alone), smoking (current/former/non smoker), persistence of MetS at phase 5 (having MetS both at phases 3 and 5), depressive symptoms, and intensity of physical activity (high/medium/low)[8] (Model 2). No significant interaction between AHEI scores and covariates (including sex) was observed. Analysis was conducted using the SAS software, version 9.1 (SAS Institute).

RESULTS

Among the 339 participants with MetS at phase 5, 158 (46.6%) recovered by phase 7. Characteristics of the participants (as a function of MetS reversion and AHEI category) are shown in Appendix-Tables A3 and A4. After controlling for potential

confounders, adherence to AHEI was associated with increased odds of MetS reversion over the 5-year follow-up (Table 1). This association was stronger among participants with MetS at both phases 3 and 5 (n of reversions/total n=56/155, OR=3.74, 95% CI:1.37-10.2). The AHEI- MetS reversion association was particularly evident among participants with central obesity and among those with high triglycerides (Table 1). Furthermore, adherence to AHEI was associated with a 5-year reversion of the high triglyceride component (n=276/767, OR=1.61, 95% CI:1.12-2.33) and with an indication of reversion of central obesity (n=75/481, OR=1.42, 95% CI:0.75-2.68). Analyses with average AHEI score across phases 3 and 5 as the exposure largely replicated these findings (Appendix-Table A5).

CONCLUSION

In the present report, we show that adherence to dietary guidance for healthy eating, the AHEI, is associated with reversion of the MetS in a middle-aged population. While several studies have investigated the diet – MetS prevalence and incidence relationships, the impact of diet on MetS reversion has only been studied in two clinical trials assessing adherence to Mediterranean-Diet in two Mediterranean countries. One trial of 180 Italian subjects found the Mediterranean -Diet intervention to led to reversion of MetS[3], the other larger trial (n=1224 Spanish) suggested that the observed effect was due to the effect of nut supplements rather than the Med-Diet as a whole[4]. Even though the clinical utility of MetS as an independent predictor of CVD has been challenged[11], our findings, from a non-Mediterranean country, are novel and strengthen evidence of the

potential impact of diet in countering increasing levels of risk factors associated with CVD and T2D.

The observed stronger impact of AHEI on MetS reversion in participants with central obesity and high triglycerides is plausible as the reduction of visceral fat[12] leads to a decrease in the flux of free fatty acids which is hypothesized to be responsible for insulin-resistance – a key feature in MetS pathophysiology[13]. This interpretation assumes that central obesity mainly reflects visceral fat as the majority of the subjects were males and there was a higher reversion of MetS in men. Further research is needed to examine these and other plausible mechanisms, such as counteracting oxidative stress (and related insulin resistance[14]) via antioxidants from fruits, vegetables and long-term multivitamin use; and the lowering of high triglyceride levels (which are linked to reduction of inflammation processes involved in MetS [15]) as a result of increased consumption of polyunsaturated fat, nuts, soy and a reduced consumption of trans fat.

Limitations of this study include: the small sample size that is not fully representative of the British population [6] and that does not allow ethnic group sub-stratification other than White/non-White, limiting the generalizability of our findings; the lack of objective measure of physical activity; and, the use of the FFQ, recognized to be less precise than diary questionnaires, to assess diet.

Despite these limitations, our findings emphasize the potential benefits of adherence to the dietary recommendations of the AHEI in middle-aged individuals with MetS, especially those with central obesity or high triglyceride levels.

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Contributors: TNA, MK, AS-M, and MGM designed the study; TNA conducted the statistical analyses and co-wrote the initial and final drafts, and is guarantor. MK, MJS, AGT, MJ, MV, MGM, JEF and AS-M co-wrote the final draft.

TNA had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

REFERENCES

- [1] Wild S, Byrne C. The Global burden of the metabolic syndrome and its consequences for diabetes and cardiovascular disease. In; Byrne CD, Wild S editors; *Metabolic syndrome*, England Wiley & Sons Ltd: 2005, p1–32.
- [2] Pedersen BK, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. *Scand J Med Sci Sports*. 2006 Feb;16 Suppl 1:3-63.
- [3] Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, D'Armiento M, D'Andrea F, Giugliano D. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *Jama*. 2004 Sep 22;292(12):1440-6.

- [4] Salas-Salvado J, Fernandez-Ballart J, Ros E, Martinez-Gonzalez MA, Fito M, Estruch R, Corella D, Fiol M, Gomez-Gracia E, Aros F, Flores G, Lapetra J, Lamuela-Raventos R, Ruiz-Gutierrez V, Bullo M, Basora J, Covas MI. Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: one-year results of the PREDIMED randomized trial. *Arch Intern Med.* 2008 Dec 8;168(22):2449-58.
- [5] McCullough ML, Feskanich D, Stampfer MJ, Giovannucci EL, Rimm EB, Hu FB, Spiegelman D, Hunter DJ, Colditz GA, Willett WC. Diet quality and major chronic disease risk in men and women: moving toward improved dietary guidance. *Am J Clin Nutr.* 2002 Dec;76(6):1261-71.
- [6] Marmot M, Brunner E. Cohort Profile: the Whitehall II study. *Int J Epidemiol.* 2005 Apr;34(2):251-6.
- [7] Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *Jama.* 2001 May 16;285(19):2486-97.
- [8] Akbaraly TN, Kivimaki M, Brunner EJ, Chandola T, Marmot MG, Singh-Manoux A, Ferrie JE. Association between metabolic syndrome and depressive symptoms in middle-aged adults: results from the Whitehall II study. *Diabetes Care.* 2009 Mar;32(3):499-504.
- [9] Brunner E, Stallone D, Juneja M, Bingham S, Marmot M. Dietary assessment in Whitehall II: comparison of 7 d diet diary and food-frequency questionnaire and validity against biomarkers. *Br J Nutr.* 2001 Sep;86(3):405-14.
- [10] Bingham SA, Gill C, Welch A, Cassidy A, Runswick SA, Oakes S, Lubin R, Thurnham DI, Key TJ, Roe L, Khaw KT, Day NE. Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. *Int J Epidemiol.* 1997;26 Suppl 1:S137-51.
- [11] Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature.* 2006 Dec 14;444(7121):881-7.
- [12] Bergman RN, Kim SP, Catalano KJ, Hsu IR, Chiu JD, Kabir M, Hucking K, Ader M. Why visceral fat is bad: mechanisms of the metabolic syndrome. *Obesity (Silver Spring).* 2006 Feb;14 Suppl 1:16S-9S.
- [13] Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005;365(9468):1415-28.
- [14] Ando K, Fujita T. Metabolic syndrome and oxidative stress. *Free Radic Biol Med.* 2009 Aug 1; 47 (3): 213-8.
- [15] Marz W, Scharnagl H, Winkler K, Tiran A, Nauck M, Boehm BO, Winkelmann BR. Low-density lipoprotein triglycerides associated with low-grade systemic inflammation, adhesion molecules, and angiographic coronary artery disease: the Ludwigshafen Risk and Cardiovascular Health study. *Circulation* 2004;110(19):3068-74.

Table 1: Association between adherence to the alternate healthy eating index (AHEI) and 5-year reversion of the metabolic syndrome (MetS).

Adherence to AHEI *, participants (n reversion cases)	Odds Ratio (95% CI) for MetS reversion	
	Model 1	Model 2
Entire cohort, N=339		
Low AHEI score, 115 (48)	1.00 (reference)	1.00 (reference)
Intermediate AHEI score, 111 (50)	1.20 (0.69, 2.08)	1.15 (0.65, 2.05)
High AHEI score, 113 (60)	1.73 (0.99, 3.02)	1.88 (1.04, 3.41)
P-value †	0.05	0.04
Subcohort: With central obesity, N = 212		
Low AHEI score, 71 (25)	1.00 (reference)	1.00 (reference)
Intermediate AHEI score, 76 (30)	1.34 (0.67 ; 2.67)	1.29 (0.61 ; 2.76)
High AHEI score, 65 (33)	2.35 (1.12 ; 4.96)	2.77 (1.19 ; 6.44)
P-value †	0.025	0.02
Subcohort: With high triglycerides, N = 294		
Low AHEI score, 103 (43)	1.00 (reference)	1.00 (reference)

Intermediate AHEI score, 92 (38)	1.07 (0.58; 1.94)	1.01 (0.54; 1.89)
High AHEI score, 99 (54)	1.92 (1.06; 3.49)	1.94 (1.04 ; 3.65)
P-value †	0.03	0.04
Subcohort: With low HDL-cholesterol, N = 198		
Low AHEI score, 65 (28)	1.00 (reference)	1.00 (reference)
Intermediate AHEI score, 60 (27)	1.00 (0.47 ; 2.12)	1.03 (0.45 ; 2.36)
High AHEI score, 73 (38)	1.37 (0.67 ; 2.81)	1.58 (0.70 ; 3.55)
P-value †	0.36	0.26
Subcohort: With hypertension, N = 279		
Low AHEI score, 98 (45)	1.00 (reference)	1.00 (reference)
Intermediate AHEI score, 90 (42)	1.09 (0.60 ; 1.99)	1.08 (0.57; 2.02)
High AHEI score, 91 (48)	1.48 (0.80; 2.73)	1.61 (0.84 ; 3.08)
P-value †	0.21	0.15
Subcohort: With high glucose, N = 131		
Low AHEI score, 39(13)	1.00 (reference)	1.00 (reference)
Intermediate AHEI score, 51 (22)	1.48 (0.59 ; 3.70)	1.41 (0.51 ; 3.89)

High AHEI score, 41 (21)	2.08 (0.80 ; 5.43)	2.52 (0.81 ; 7.88)
P-value †	0.13	0.11

Metabolic syndrome defined using the NCEP definition (7) based on the presence of 3 or more of the following: waist circumference: men >102 cm, women >88 cm; serum triglycerides: ≥ 1.7 mmol/L; HDL cholesterol: men <1.04 mmol/L, women < 1.29 mmol/L; blood pressure: ≥ 130 mmHg / ≥ 85 mmHg systolic over diastolic pressure; fasting glucose: ≥ 6.1 mmol/L or presence of T2D. Waist circumference was taken as the smallest circumference at or below the costal margin. Resting blood pressure was measured with the participant seated using the Hawksley Random Zero Sphygmomanometer (phase 3 and 5) and the OMRON HEM 907 (phase 7). Serum triglycerides, HDL cholesterol and fasting blood glucose were analyzed as previously described.(8)

*Low AHEI adherence: median score =39.5, range 13.5-43.5; Intermediate AHEI adherence: median score =50.5, range 44.5-55.5; High AHEI adherence: median score =62.5, range 56.5-76.5.

† P value of the comparison between high vs. low AHEI score.

Model 1: Adjusted for sex, age, ethnicity and energy intake.

Model 2: Model 1+ additionally adjusted for education, marital status, smoking habits, physical activity, persistence of the metabolic syndrome, and depressive symptoms.