

Hypertriglyceridemic-Waist Phenotype is a Useful Global Assessment Tool for Predicting Acute Myocardial Infarction

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Abstract

Background: There has been growing research interest in exploring the utility of the hypertriglyceridemic-waist phenotype as a predictor of cardio-metabolic risk. To date, prospective studies evaluating the phenotype as a predictor of cardiovascular disease have provided variable results.

Objectives: To evaluate the usefulness of the hypertriglyceridemic-waist phenotype as an independent predictor of acute myocardial infarction beyond classical cardiovascular disease risk factors in a homogeneous Norwegian population.

Methods: Norwegian health survey (Cohort Norway) participants (n=116,111), free of heart disease in 1994-2003, were followed through 2009 by record linkages to The Cause of Death Registry and hospital discharge diagnoses through the Cardiovascular disease in Norway project. Cox proportional hazards analyses adjusted for conventional risk factors.

Results: During a mean follow-up of 11.5 yrs (SD=2.8), 3,624 participants developed an acute myocardial infarction. Prevalence of an enlarged waist (>102 cm for men, and >88 cm for women) increased from the lowest to highest quartile of triglycerides for men (4.9% to 22.5%) and women (6.5% to 42.1%; P for trend < 0.01). The presence of an enlarged waist and elevated triglyceride (>1.7 mmol/L) was associated with a hazard ratio for acute myocardial infarction of 1.68 (95% CI 1.48-1.90) for men and 1.95 (95% CI 1.66-2.29) for women compared to those with normal waist and triglyceride level after adjusting for age, smoking and time since last meal. However, 75% of the excess risk was mediated by HDL and nonHDL cholesterol.

Conclusions: The phenotype is a useful global assessment tool but of limited value when conventional risk factors are available. Patients presenting with the phenotype should be targeted with lifestyle interventions and referred for clinical follow-up.

Keywords: Hypertriglyceridemia; Central obesity; Cardiovascular disease

Abbreviations: AMI: Acute Myocardial Infarction; CONOR: Cohort Norway; CVD: Cardiovascular Disease; CVDNOR: Cardiovascular Disease in Norway Project; ICD: International Classification of Diseases; HDL-C: High-Density Lipoprotein Cholesterol; HR: Hazard Ratio; LDL-C: Low-Density Lipoprotein Cholesterol

Introduction

The presence of hypertriglyceridemia with an elevated waist circumference, referred to as the hypertriglyceridemic-waist phenotype, is considered a proxy indicator of visceral fat which is now recognized to have greater metabolic consequences than that attributed to subcutaneous fat alone [1]. The phenotype has also been proposed to be a simpler alternative to the metabolic syndrome, and there has, therefore, been growing research interest in exploring the utility of the hypertriglyceridemic-waist phenotype as a predictor of cardiometabolic risk [2]. Numerous studies have identified the phenotype as being a strong associate and determinant of insulin resistance and diabetes in cross-sectional and prospective studies [3-7]. While a few prospective studies have evaluated the association between the phenotype and cardiovascular disease (CVD), the results of these studies are highly variable [8-12]. Thus, the usefulness of the phenotype as an independent predictor of CVD beyond classical CVD risk factors is not yet established.

In addition, data suggest that non-fasting triglycerides correlate

strongly with post-prandial remnant lipoproteins, and that non-fasting triglycerides are superior to fasting triglycerides in characterizing the usual post-prandial state and its associated risks [13,14]. Also, it is the remnant lipoproteins associated with elevated triglycerides and not the triglycerides, per se, that are considered atherogenic [15,16]. The presence of an enlarged waist with elevated triglyceride levels could identify individuals unable to clear and store excess triglycerides from over-nutrition and, therefore, identify individuals who are more likely to be chronically exposed to elevated remnant lipoproteins than individuals without the phenotype [1].

Given the strong association of the hypertriglyceridemic-waist phenotype with insulin resistance and that elevated non-fasting triglycerides associate with greater exposures to atherogenic remnant lipoproteins, we evaluated, prospectively, the risk of incident acute

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myocardial infarction (AMI) by the hypertriglyceridemic-waist phenotype in a large population-based cohort in Norway.

Material and Methods

Participants in at least one population-based regional health screening of Cohort Norway (CONOR) between 1994 and 2003 formed the baseline of the prospective study, details of which are described elsewhere [17,18]. Of a total of 309,742 invitations for CONOR study participation, 59% (181,891) participated, of whom 173,243 men and women attended at least one health screening. Participants with a self-reported history of heart disease, stroke, angina, and current or past use of antihypertensive medications or with missing baseline health information (n=32,453) were excluded, leaving a total of 140,790 participants for analyses. Missing data for covariates was low for the majority of parameters (< 1% for smoking, lipids, and blood pressure, 4.9% for time since last meal, and 8.8% for alcohol consumption), but waist circumference measures were missing for 17.4% of the study population as it was not included in one regional survey. After exclusion of participants with missing data, 116,111 participants had a baseline assessment of non-fasting triglycerides and waist circumference.

An 11-digit personal identifier was used to identify status of CONOR participants as of December 31, 2009 through records linkages with the Cause of Death Registry and national hospital discharge diagnoses which were obtained through the Cardiovascular Disease in Norway Project (CVDNOR), 1994-2009 [18-20]. Only 0.8% of the cohort was lost to follow-up due to migration. The outcome for the current analyses was hospitalization or death attributed to the first registered AMI occurring between baseline through 2009 using the International Classification of Diseases (ICD) codes of 410 (ICD-9) and I21 and I22 (ICD-10). Informed consent was obtained from each participant and the study protocol conforms to the ethical guidelines of the Declaration of Helsinki as reflected in a priori approval by the Regional Ethics Committee which approved both the baseline survey and the prospective record linkages.

Non-fasting triglycerides, total and HDL-C were measured by an enzymatic method (Boehringer 148393, Boehringer-Mannheim, Federal Republic of Germany from 2000 Hitachi 917 auto analyzer, Roche Diagnostic, Switzerland). NonHDL-C was calculated as total-C minus HDL-C. The average of three systolic and diastolic blood pressure readings taken after a 2 min rest by an automatic device (DINAMAP, Criticon, Tampa, FL, USA) was used in analyses. Enlarged waist was defined as having a waist circumference > 102 cm for men and > 88 cm for women [21].

Statistical Analyses

Baseline demographic characteristics were evaluated for men and women using X² and t-tests for differences in proportions and means comparing those with and without an enlarged waist circumference. Sex-specific quartiles of triglycerides were created to facilitate presentation of data. Previously we reported the cardiovascular risk factor levels by sex-specific triglyceride quartiles for men and women in the larger cohort in which we found that all risk factors were more adverse with increasing triglyceride quartiles: as the results were similar when restricted to those with an available waist circumference measure, these data are not presented in the current report [18].

AMI rates per 10,000 person-years were age-adjusted based upon 5-year age intervals, using the study's age distribution as the standard population. Age-adjusted rates of AMI were compared between those with and without an enlarged waist within each triglyceride quartile.

Age-adjusted and multivariable Cox proportional hazard analyses were conducted separately for men and women and results presented as Hazard Ratios and 95% confidence intervals (CI). Proportional hazard assumption was evaluated by Schoenfeld's test. An elevated waist circumference (yes vs. no) by triglyceride level interaction term was tested in age and multivariable adjusted analyses where triglyceride levels were evaluated using several approaches: as mmol/L, sex-specific quartiles, and as high vs. low (< 1.7 vs. > 1.7 mmol/L). We conducted stratified analyses in which we evaluated adjusted HRs by stratum of enlarged waist (yes vs. no) and elevated triglyceride (>1.7 mmol/L). We also conducted the above mentioned analyses using a triglyceride cut-off of > 2.0 mmol/L, but as all results were similar they are not presented.

Multivariable models considered time since last meal (hrs) and conventional risk factors at baseline: age (yrs), current daily smoking (yes vs. no), systolic blood pressure (mm Hg), self-reported diabetes (yes vs. no), HDL-C and nonHDL-C (mmol/L), and frequency of alcohol consumption (> once a week, once per week, two-three times per month, once per month or less). The percentage of excess risk associated with the hypertriglyceridemic-waist phenotype that was mediated by HDL-C and nonHDL-C was evaluated as follows:

$$\left[\frac{(\text{HR (smoking and age adjusted)} - \text{HR (smoking, age, HDL-C and nonHDL-C adjusted)})}{\text{HR (smoking and age adjusted)} - 1} \right] \times 100 \text{ [22].}$$

Significance was determined by $P < 0.05$. Stata 12 (StataCorp LP, College Station, Texas) was used in all analyses.

Results

At baseline, the average age was 47.4 yrs (SD=14.3) for men and 46.3 yrs (SD=14.1) for women and an enlarged waist was present for 13% of men and 21.5% of women. For men and women, those with an enlarged waist were, on average, 5-6 years older, more likely to have diabetes, and less likely to be smokers or to have any college education (Table 1). All baseline cardiovascular risk factors were more adverse among those with an enlarged waist (all P-values < 0.0001). The time since last meal ranged from 0 to 8 hours in which 84.8% had a time since last meal of 4 hours or less. For each quartile and decile of triglycerides, the median time since last meal was 2 hours (IQR was 1-3 hours).

The mean follow-up time was 11.5 yrs (SD=2.8) for both men and women. A total of 2,537 (4.6%) men and 1,086 (1.8%) women developed an AMI. In stratified analyses in which normal and elevated triglyceride levels were evaluated by the presence and absence of an enlarged waist, we observed that the HRs associated with the presence of both conditions in men (who had a 68% excess risk) and women (who had a 95% excess risk) reflected what would be expected assuming an additive effect of having an enlarged waist and an elevated triglyceride level (model 1, Table 2). After further adjustment for HDL and nonHDL-C (model 2), the HR were considerably attenuated with 75% of the excess risk associated with the phenotype being mediated by HDL-C and nonHDL-C. With adjustment for additional risk factors, no significant association with AMI was observed for elevated triglycerides, enlarged waist or for having both conditions vs. none (model 3, Table 2). Further, there was no significant enlarged waist circumference (yes vs. no) by triglyceride multiplicative interaction term in age-adjusted or multivariable adjusted analyses in men and women.

In age-adjusted analyses (not presented in the tables), an enlarged waist circumference was associated with greater age-adjusted HRs for

	MEN		WOMEN	
	Waist		Waist	
	Normal	Enlarged ^{b,c}	Normal	Enlarged ^{b,c}
No. Participants	48,309	7,251	47,556	12,995
Age (yrs)	47.2 (14.3)	52.2 (14.6)	45.4 (13.5)	51.0 (14.7)
nonHDL-C (mmol/L)	4.44 (1.13)	4.91 (1.07)	4.00 (1.16)	4.73 (1.21)
HDL-C (mmol/L)	1.27 (0.34)	1.13 (0.30)	1.55 (0.39)	1.35 (0.35)
Triglycerides (mmol/L)	1.86 (1.20)	2.55 (1.56)	1.25 (0.75)	1.93 (1.13)
% Diabetes	1.5	3.6	0.8	3.3
Glucose (mmol/L)	5.36 (1.32)	5.78 (1.81)	5.11 (1.00)	5.52 (1.59)
% Current smokers	31	28	33	29
BMI (kg/m ²)	25.5 (2.7)	31.3 (3.3)	23.9 (2.9)	31.0 (4.1)
Waist circumference (cm)	89 (6.9)	108 (6.4)	76 (6.5)	96 (7.6)
SBP (mm Hg)	134 (16.5)	141 (18.2)	125 (18.4)	137 (21.6)
DBP (mm Hg)	78 (10.6)	83 (13.1)	73 (10.7)	78 (11.7)
% any college education	32	25	33	21

^aData presented as means (SD) unless designated as percent (%)

^bDefined as > 102 cm for men and > 88 cm for women

^cDifferences in all characteristics presented between normal and enlarged waist circumference groups are statistically significant with P < 0.0001

Abbreviations: nonHDL-C: nonhigh-density-lipoprotein cholesterol; HDL-C: high-density-lipoprotein cholesterol; BMI: body mass index; SBP and DBP: systolic and diastolic blood pressure, respectively.

Table 1: Baseline characteristics of study population by presence or absence of an enlarged waist circumference: Cohort Norway^a.

	Normal Waist		Enlarged Waist ^a	
	Low Triglyceride < 1.7 mmol/L	Elevated Triglyceride ≥1.7 mmol/L	Low Triglyceride < 1.7 mmol/L	Elevated Triglyceride ≥1.7 mmol/L
MEN				
No. of Participants	27,049	21,259	2,267	4,984
No. of cases	983	1,081	130	343
HR, model 1 ^b	1.0	1.45 (1.32-1.58)	1.16 (0.95-1.41)	1.68 (1.48-1.90)
HR, model 2 ^c	1.0	1.09 (0.98-1.20)	1.05 (0.86-1.27)	1.17 (1.02-1.35)
HR, model 3 ^d	1.0	1.07 (0.96-1.19)	1.01 (0.82-1.25)	1.14 (0.99-1.32)
WOMEN				
No. of Participants	38,959	8,597	6,639	6,356
No. of cases	405	272	136	273
HR, model 1 ^b	1.0	1.55 (1.32-1.82)	1.30 (1.06-1.59)	1.95 (1.66-2.29)
HR, model 2 ^c	1.0	1.03 (0.86-1.23)	1.16 (0.95-1.43)	1.24 (1.03-1.49)
HR, model 3 ^d	1.0	1.06 (0.86-1.30)	1.12 (0.88-1.43)	1.11 (0.89-1.39)

^a for men ≥ 102 cm for women ≥ 88 cm

^b model 1: baseline age (yrs), current daily smoking (yes vs. no), time since last meal (hrs).

^c model 1 plus HDL-C and nonHDL-C (mmol/L).

^d model 1 plus HDL-C and nonHDL-C (mmol/L) and systolic blood pressure (mmHg), self-reported diabetes (yes vs. no), and frequency of alcohol consumption in past year (>1 week, 1 per week, 2-3 times per month, 1 per month or less).

Table 2: Age and multivariable adjusted hazard ratios (95% CI) for incident acute myocardial infarction by the presence or absence of an enlarged waist and elevated triglyceride level: Cohort Norway.

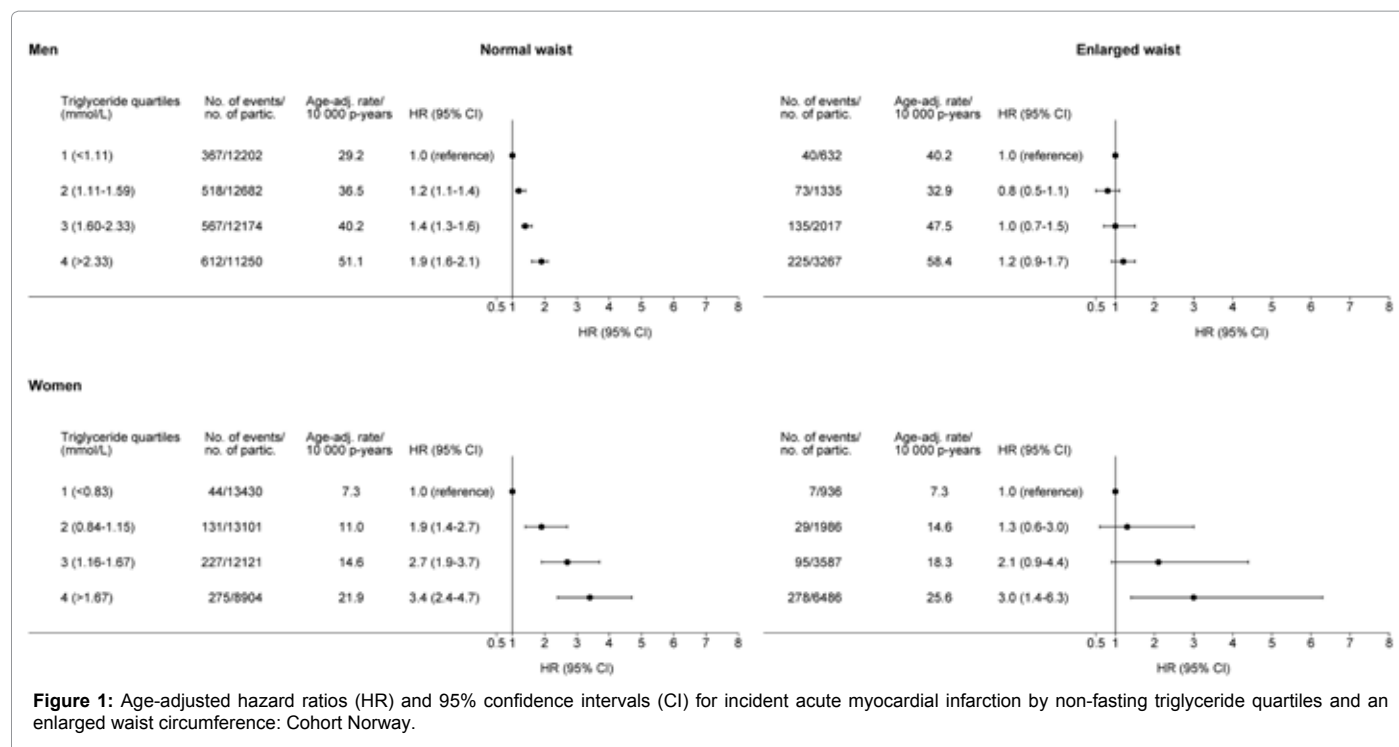
AMI for both men (HR = 1.2; 95% CI 1.1 – 1.4) and women (HR = 1.4; 95% CI 1.2 – 1.6). However, an enlarged waist did not predict AMI in multivariable models considering conventional risk factors in men (HR = 1.0; 95% CI 0.9 – 1.1) or in women (HR = 1.1; 95% CI = 0.9 – 1.2). Further, in analyses stratified by sex-specific quartiles of triglycerides, only modest additional risk was associated with an enlarged waist circumference in men and women (Figure 1). To illustrate, for men in the highest triglyceride quartile (>2.33 mmol/L), age-adjusted AMI rates were 58.4 and 51.1 per 10,000 person years for those with and without an enlarged waist, respectively (HR=1.1; 95% 0.9-1.3) (Figure 1). In women in the highest sex-specific triglyceride quartile (>1.67 mmol/L), age-adjusted AMI rates were 25.6 and 21.9 per 10,000 person years for those with and without an enlarged waist, respectively (HR=1.17; 95% CI= 1.04 – 1.45, P=0.02). These differences were no longer significant after considering conventional risk factors. However, we do note wide confidence intervals with increasing triglyceride quartiles for women with an enlarged waist (Figure 1).

Conclusions

The presence of the hypertriglyceridemic-waist phenotype was associated with increased risk of AMI with stronger associations noted for women than for men. We found that the majority of excess risk associated with having both conditions, compared to neither condition, was mediated through HDL-C and nonHDL-C. HDL-C and nonHDL-C are both highly related to triglyceride levels and to an enlarged waist circumference [17]. Also, HDL-C and nonHDL-C provide important information about underlying lipoprotein metabolism in which the need for additional consideration of triglyceride levels becomes less important [23]. Further, when additional risk factors were considered, the phenotype and stratum-specific combinations of enlarged waist and elevated triglycerides were of no value in the prediction of AMI.

Strengths and Limitations

Strengths of our study include the large community-dwelling



cohort and the assessment of nonfasting triglyceride levels which is now considered superior to fasting triglycerides in predicting coronary heart disease [13]. Also, while we were not able to adjust for LDL-C, we did include nonHDL-C and HDL-C in our multivariable models, which is another strength of the study given that nonHDL-C may be a stronger risk factor than LDL-C in risk prediction and that there is evidence that HDL-C and nonHDL-C, or the ratio of total cholesterol to HDL-C, are more closely related than LDL-C to the atherogenic dyslipidemia observed in obesity [23-26]. Another important strength is the comprehensive ascertainment of follow-up case status through record linkages with hospital discharge diagnoses and the Cause of Death Registry. Given the homogenous ethnic Norwegian study population, one limitation is that our results are not generalizable to other ethnic/racial groups.

Results of other prospective studies have provided mixed results, likely reflecting differences in definitions of the phenotype, characteristics of the population studied, sample size, and the extent to which analyses adjusted for important covariates [8-12]. In a cohort of 557 postmenopausal Danish women followed for 8.5 years, the presence of both an enlarged waist (>88cm) and elevated fasting triglycerides (> 1.45 mmol/L), when compared to those without the phenotype, conveyed a 4.7-fold increased risk for CVD mortality based upon 36 deaths, adjusting for age, smoking, and low-density lipoprotein cholesterol [11]. In the Tehran Lipid and Glucose study, 6,834 men and women were followed for an average of 9.3 years in which the presence of the phenotype significantly predicted incident CVD among women (HR of 1.47, 95% CI 1.11-1.94), but not men, in analyses adjusting for a number of risk factors including the Framingham risk score [10]. In the EPIC-Norfolk Prospective Population Study of 21,787 participants followed for a mean of 9.8 years, sex differences were noted in the relative importance of the phenotype in predicting coronary artery disease [8]. In women, but not men, those with both an enlarged waist and elevated triglyceride level were at significantly

greater risk for incident CVD (adjusted HR of 1.67) when compared separately to all other strata of enlarged waist with or without an elevated triglyceride level. However, in additional analyses considering the Framingham risk score, the presence of the phenotype significantly predicted coronary artery disease only among those in the lowest risk tertile of the Framingham risk score [8]. In 3,430 male participants of an intervention trial of antioxidant supplementation (SU.VI.MAX study) prospectively followed for a mean of 7.5 years, the phenotype of an enlarged waist and elevated triglyceride level conveyed a 2.1-fold increased risk for incident CVD among men when compared to those with normal waist circumference and triglyceride levels, adjusting for age, smoking, blood pressure, physical activity and fasting glucose, but not lipids [9]. In the large population-based Chinese cohort (the Kailuan Study) of 76,605 men and 19,410 women with a mean follow-up period of 4 years, the presence of the phenotype (>90 cm waist and > 2.0 mmol/L fasting triglyceride and >85 cm waist and > 1.5 mmol/L triglyceride for men and women, respectively) was associated with a HR of 1.24 (95% CI 1.07-1.44) for CVD after adjusting for conventional risk factors [12]. In a 5 year follow-up of 5,924 cardiovascular patients, evaluating the lipid accumulation product based upon triglyceride and waist circumference measures, unadjusted analyses identified the phenotype to be a significant predictor of mortality in women but not men; but results were attenuated and not significant in analyses adjusting for other risk factors [27].

Despite differences in study results, there is a tendency in the literature for an enlarged waist and an elevated triglyceride level to be a more important predictor of CVD in women than in men: findings which are compatible with our current study results. In a prior analysis of the same study population, we identified a stronger gradient in risk of AMI associated with deciles of nonfasting triglyceride values in women compared to men [18]. Also, we noted increasingly wider confidence intervals for HRs for AMI associated with increasing triglyceride quartiles for women with an at-risk waist circumference. Elevated

triglyceride levels precede the development of diabetes, and central fat patterning associates with insulin resistance [28]. Also of note, is that diabetes is a stronger risk factor for CHD in women compared to men [29]. These considerations may explain the sex differences observed in the current study and in the literature.

Our findings do not support any additional value of incorporating assessment of an enlarged waist with an elevated nonfasting triglyceride value in CHD risk prediction when conventional risk factors are available. WHO's Expert Consultation on metabolic syndrome has emphasized its limited utility [30]. Indeed, with nearly three decades of research behind us, beginning with the related concept of Syndrome X, which then led to the initial metabolic syndrome definition, the syndrome has not found its place in medical practice as a management or diagnostic tool [31]. Our current study evaluating the simple alternative to the metabolic syndrome, the hypertriglyceridemic-waist phenotype, suggests that it has no utility in terms of CHD risk prediction when conventional risk factors are available.

However, our findings do suggest that the phenotype is a useful global prediction tool, particularly for women. Patients presenting with the phenotype should be referred for standard clinical evaluation and treatment of CVD risk factors, as needed, and importantly they should be targeted with lifestyle interventions designed to increase physical activity and to improve dietary habits. The findings also suggest that further work is needed to explore the utility of the phenotype in CHD prediction in women given the wide confidence intervals for the HRs identified in women in the current study and the stronger associations observed for the phenotype in women compared to men in the literature.

Conflicts of Interest

The authors declare no conflicts of interest.

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