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Metabolic syndrome and its components are associated with non-arteritic anterior ischaemic optic neuropathy

Darrell Kohli,[1] Kristi Y Wu,[1] Launia J White,[2] David O Hodge,[2] John J Chen,[1,3] Gavin W Roddy [1]

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[1]Mayo Clinic, Rochester, Minnesota, USA
[2]Quantitative Health Sciences, Mayo Clinic, Jacksonville, FL, USA
[3]Department of Neurology, Mayo Clinic, Rochester, MN, USA

Correspondence to
Dr Gavin W Roddy; roddy.gavin@mayo.edu

ABSTRACT

Purpose To determine whether metabolic syndrome (MetS) is a risk factor for various forms of optic neuropathy including non-arteritic anterior ischaemic optic neuropathy (NAION).

Methods This population-based analysis identified patients ≥40 years of age in Olmsted County, Minnesota, USA using the Rochester Epidemiology Project 2005–2018. Patients with MetS were identified if three or more of the five standard criteria for diagnosing MetS were present: systemic hypertension, hyperglycaemia, hypertriglyceridaemia, reduced high-density lipoprotein cholesterol (hypoalphalipoproteinaemia) and central adiposity defined by increased body mass index. Charts of patients identified as having an optic neuropathy were reviewed to record specific diagnoses and compared with patients without ocular pathology other than cataract. The odds ratio (OR) of association with MetS was calculated and adjusted for age, sex and race with multivariate analysis for the various optic neuropathies.

Results Patients with MetS were more likely to have an optic neuropathy than those without (OR 2.2, p<0.001). After adjusting for age, sex and race, the only optic neuropathy found to be significantly associated with MetS was NAION (OR 6.17, p=0.002). For patients with NAION, though each individual component of MetS was individually significantly associated with MetS, further analysis suggested that hypertriglyceridaemia, hypoalphalipoproteinaemia and hyperglycaemia were likely the key drivers in the overall significance between NAION and MetS.

Conclusion Patients with MetS were more likely to have NAION. Further studies are needed to determine whether MetS is a modifiable risk factor for NAION.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Metabolic syndrome (MetS) is a constellation of findings that includes systemic hypertension, hyperglycaemia, hypertriglyceridaemia, reduced high-density lipoprotein cholesterol and central adipositythat leads to significant health consequences. Though individual components of MetS were previously associated with non-arteritic anterior ischaemic optic neuropathy (NAION), little was known about the association of MetS with NAION.

WHAT THIS STUDY ADDS

⇒ In a population-based study, we found that MetS is associated NAION highlighting the potential importance of systemic disease management on ocular health.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ MetS may be a modifiable risk factor for NAION; therefore, further studies are needed to determine whether treatment of MetS may reduce the incidence of NAION.

INTRODUCTION

Metabolic syndrome (MetS) is a constellation of clinical and metabolic factors that is a significant contributor to morbidity and mortality with great physical and economic costs to individuals and healthcare systems.[1 2] MetS increases the risk of cardiovascular disease by two-fold, type 2 diabetes by five-fold, and is a risk factor for increased all-cause mortality.[3–5] The public health implications of MetS are significant, with uptrending rates over recent decades and overall prevalence estimates of almost 35% in the USA,[6] with even higher rates in other countries.[3 7] Though minor variations in diagnostic criteria exist, three or more of the following five conditions are generally required for a diagnosis of MetS: impaired fasting glucose (hyperglycaemia), truncal obesity, low high-density lipoprotein(HDL), cholesterol (hypoalphalipoproteinaemia), elevated triglyceride levels (hypertriglyceridemia) and elevated blood pressure (systemic hypertension).[3 4]

Understanding the summation of metabolic stresses in an individual is a challenge with multiple variables related to diet, exercise and other comorbidities. MetS is a definable phenotype that identifies individuals at risk of end organ damage related to metabolic stress.[8] At the cellular level, MetS is associated with a chronic inflammatory state and elevated oxidative stress.[9–11] A growing body of evidence demonstrates MetS is a contributor to age-related eye disease.[8 12 13] This finding

is supported by studies in animal models,[14 15] and mechanisms proposed are related to chronic inflammatory and oxidative stress.[8 14–16] The relationship to the risk of developing glaucomatous optic neuropathy (GON) has been studied, with some reports demonstrating a positive association[17–20] though we recently found no association with GON and MetS using a population-based cohort.[21] Reports detailing the association between MetS and non-GONs, including non-arteritic anterior ischaemic optic neuropathy (NAION), are lacking and limited to case series level of evidence.[22]

NAION occurs secondary to acute hypoperfusion, or a disruption in microcirculation, which results in an ischaemic insult and swelling of the optic nerve.[23–25] NAION is multifactorial with multiple risk factors identified, including the individual components of MetS: systemic hypertension,[23 24 26–28] diabetes mellitus,[23 24 26 28–30] hypoalphalipoproteinaemia,[31 32] hypercholesterolaemia[23 28 29 33 34] and hypertriglyceridaemia.[28 33] Furthermore, chronic obstructive sleep apnoea,[23 24 28 35 36] transient hypotension[23 24] and small cup to disk ratio[23 24] are also risk factors for NAION. The optic nerve's susceptibility to conditions of inflammation and disruptions in microcirculation is an object of interest in terms of the chronic, deleterious effects of MetS. Here, we used the Rochester Epidemiology Project (REP), which provides shared medical records in Olmsted County, Minnesota, USA with permission to researchers,[37] to determine the population-based risk of MetS with various forms of optic neuropathy including NAION.

METHODS

Participants and data collection

Patients in Olmsted County, Minnesota, USA, were identified using the REP database aged 40 years and over with at least one eye exam who were residents of Olmsted County, Minnesota, USA between 1 January 2005 and 31 December 2018.[21] Initially, only the diagnosis code for MetS (ICD-10 E88.81) was used for defining the condition, which resulted in a prevalence of only 6.15%.[21] With MetS having a much higher prevalence in the general population,[6] we used the established diagnostic criteria for MetS in order to identify patients with MetS using raw data as previously described.[21] Therefore, in addition to the MetS diagnosis code, we used laboratory values and/or medication use to treat the specific condition in order to determine whether a patient had three or more of the five standard criteria required for the diagnosis of MetS: systemic hypertension with median blood systolic blood pressure ≥130 mm Hg or median diastolic blood pressure ≥85 mm Hg diastolic or medical treatment for systemic hypertension, hyperglycaemia with two independent readings of fasting glucose ≥100 or medical treatment for hyperglycaemia, hypertriglyceridaemia with two independent readings of triglycerides ≥150 mg/dL or medical treatment of hypertriglyceridaemia, hypoalphalipoproteinaemia with two independent readings of HDL <40 mg/dL in men and <50 mg/dL in women or medical treatment of hypoalphalipoproteinaemia and central adiposity defined by body mass index (BMI) ≥27 kg/m^2.[21] Criteria used were in accordance with the definition formed by the International Diabetes Federation and American Heart Association/National Heart, Lung and Blood Institute.[38] Electronic medical records were reviewed to identify specific optic neuropathies. Forms of optic neuropathy included were: arteritic optic neuropathy (ICD-10 code M31.6), NAION (ICD-10 code H47.019), optic neuritis (International Classification of Diseaseses-10 (ICD-10) code H46.9), optic disc drusen (ODD, ICD-10 code H47.392), diabetic papillitis (ICD-10 code H46.00), papilloedema (ICD-10 code H47.10), compressive, congenital (ICD-10 code Q14.2), toxic (ICD-10 code H46.3), radiation, traumatic and disc pallor or atrophy of unknown aetiology. Our control group was identified as patients who presented for a routine eye exam without an ocular diagnosis other than cataract or refrative error. The records were reviewed to confirm the optic neuropathy diagnosis based on history, exam findings and imaging.

Statistical analysis

The primary outcome of interest was whether the presence of an optic neuropathy, including NAION, was associated with the presence of MetS or its components. Each patient was categorically labelled as having a particular diagnosis, then the rate of each condition was calculated using a percentage value, OR were calculated and Fisher's exact tests were performed to compare each group. For the analysis of MetS and each of the components, multivariate logistic regression models were performed adjusting for age, sex and race. P values <0.05 were deemed significant unless otherwise specified when a Bonferroni correction was applied for multiple comparisons. Statistical analysis was performed using SAS V.9.4.

RESULTS

Demographics

A higher median age was present in patients with MetS compared with patients without MetS (65.0 vs 55.0, p<0.001, table 1). Male sex was a minority in both groups, but higher in patients with MetS (48.1% vs 26.4%, p<0.001, table 1). Patients with MetS and without MetS self-identified as primarily white, however, a higher proportion of white patients were present in the MetS group (91.9% vs 90.3%, p<0.001, table 1).

Rates of optic neuropathies in patients with Mets and NO Mets

Thirty-five of 6986 (0.5%) patients had an optic neuropathy in the non-MetS group and 287 of 22 399 (1.3%) patients had an optic neuropathy in the MetS group (OR 2.20, p<0.001, table 2). Of the optic neuropathy diagnoses, after adjusting for age, sex and race, only NAION (96/22 399, 0.4% vs 3/6986, 0.0%, OR 6.17, p=0.002) was found to be significantly associated with MetS (table 2). There was a trend of an association between optic neuritis

Table 1 Baseline demographic data

Characteristic	N	No of metabolic syndrome Median (minimum, maximum) or N (%)	N	Metabolic syndrome Median (minimum, maximum) or N (%)	P value
Age at last eye exam	6986	55.0 (40.0, 101.0)	22399	65.0 (40.0, 104.0)	<0.001
Sex, male	6986	1845 (26.4)	22399	10771 (48.1)	<0.001
Race, white	6900	6230 (90.3)	22070	20292 (91.9)	<0.001

(21/22 399, 0.1% vs 2/6986, 0.0%, OR 4.78, p=0.04) and MetS, but this was no longer significant after Bonferroni correction for multiple variables. ODD, giant cell arteritis, diabetic papillitis, papilloedema, compressive optic neuropathy, congenital optic neuropathy, toxic optic neuropathy, radiation optic neuropathy, optic pallor or atrophy of unknown aetiology or traumatic showed no association with MetS (table 2).

Association of NAION with Mets and its components

Individual components of MetS were analysed to determine potential association with NAION. A higher proportion of patients with BMI ≥27 kg/m^2 (OR 1.84, p=0.014), hypertriglyceridaemia (OR 5.63, p<0.001), hypoalphalipoproteinaemia (OR 6.86, p=0.001), systemic hypertension (OR 2.19, p=0.016) and hyperglycaemia (OR 2.22, p=0.005) had NAION, suggesting that each individual component of MetS has some risk association with NAION (table 3). In order to determine whether increasing numbers of individual MetS components led to an increased risk of NAION, the data were analysed in a stepwise fashion. Starting with two MetS components, there was a trend with each additional individual MetS component was associated with an increased risk of NAION: two components (1/99 vs 2038/29 286, OR 0.97, p=0.98), three components (9/99 vs 5095/29,286, OR 3.17, p=0.28), four components (26/99 vs 7382/29,286, OR 5.42, p=0.10) and five components being statistically significant (61/99 vs 9826/29 286, OR 8.58, p=0.035).

To evaluate whether the strongest association was MetS itself or certain MetS components, the relationship between NAION and individual component variables, including MetS treated as a single component, was analysed (table 4). Comparing two variables alone enabled a determination of one variable while controlling for the second variable in order to determine the weight of association of one component in comparison to another. A number of components of MetS lost significance with controlling for a second variable. The remaining significant associations even when controlling for the second variable may indicate the strongest associations. For example, BMI ≥27 kg/m^2 remained significantly associated with NAION when controlling for systemic hypertension (OR 1.68, p=0.040) and systemic hypertension remained significant when controlling for BMI ≥27 kg/m^2 (OR 1.94, p=0.045). Hypertriglyceridaemia remained significantly associated with NAION after controlling for BMI ≥27 kg/m^2 (OR 4.96, p=0.002), systemic hypertension (OR 4.95, p=0.002), hyperglycaemia (OR 4.88, p=0.002). Hypoalphalipoproteinaemia remained significantly associated with NAION after controlling for BMI ≥27 kg/m^2 (OR 6.00, p=0.003), systemic hypertension (OR 5.99, p=0.003) and hyperglycaemia (OR 5.91, p=0.003). Hyperglycaemia remained significantly associated with NAION after controlling for BMI ≥27 kg/m^2 (OR 1.99, p=0.016), hypertriglyceridaemia (OR 1.84, p=0.029), hypoalphalipoproteinaemia (OR 1.83, p=0.031) and systemic hypertension (OR 1.99, p=0.016).

MetS as a whole was no longer associated with NAION after controlling for hypertriglyceridaemia (OR 2.78, p=0.15) or hypoalphalipoproteinaemia (OR 2.49, p=0.21). However, MetS remained significantly associated with NAION after controlling for BMI ≥27 kg/m^2 (OR 5.31, p=0.006), systemic hypertension (OR 5.33, p=0.007) and hyperglycaemia (OR 4.98, p=0.008). Therefore, no component is highlighted as the sole influencer in the association seen between MetS and NAION. This analysis suggests, however, that BMI ≥27 kg/m^2 and systemic hypertension play minor roles in the overall association with MetS and NAION, and that hypertriglyceridaemia, hypoalphalipoproteinaemia and hyperglycaemia play more significant roles in the overall association observed between MetS and NAION.

DISCUSSION

In this population-based study, we found that patients with MetS were more likely have NAION after adjusting for age, sex and race compared with those without MetS. Given the strongest association with NAION, we selected the association with MetS and NAION for further study. Each individual component of MetS was associated with NAION when examined as stand-alone risk factor and the risk of NAION increased with increasing individual components of MetS. Of the components, our data suggest that BMI ≥27 kg/m^2 and systemic hypertension play minor roles while hypertriglyceridaemia, hypoalphalipoproteinaemia and hyperglycaemia are likely the most significant contributors to the overall association between MetS and NAION.

NAION is an event that is thought to be caused by acute hypoperfusion of the optic nerve head secondary to a number of etiologies including vascular dysregulation or vasospasm, systemic hypotension, nocturnal hypotension or a thrombotic event.[23–25] Impaired vascular, proinflammatory and prothrombotic states caused by lipid derangements[39–41] increase the optic nerve's susceptibility to these hypoperfusion events. Similar pathological pathways are dysregulated

Table 2 Association between metabolic syndrome and various forms of optic neuropathy

Association between metabolic syndrome and	No of metabolic syndrome N (%), N=6986	Metabolic syndrome N (%), N=22 399	Association measure	Unadjusted analysis		Adjusting for age, sex and race	
				Estimate (95% CI)	P value	Estimate (95% CI)	P value
No of eye disease	6951 (99.5)	22 112 (98.7)	OR	1.00 (reference)	N/A	1.00 (reference)	N/A
Optic neuropathy	35 (0.5)	287 (1.3)		2.58 (1.81 to 3.67)	<0.001	2.20 (1.51 to 3.20)	<0.001
NAION	3 (0.0)	96 (0.4)	OR	9.99 (3.17 to 31.51)	<0.001	6.17 (1.92 to 19.85)	0.002
Optic disk drusen	14 (0.2)	47 (0.2)	OR	1.05 (0.58 to 1.90)	0.88	0.87 (0.46 to 1.67)	0.68
Optic neuritis	2 (0.0)	21 (0.1)	OR	3.27 (0.77 to 13.96)	0.11	4.78 (1.07 to 21.26)	0.040
Giant cell arteritis	0 (0.0)	12 (0.1)	OR	7.78 (0.41 to 147.11	0.17	2.12 (0.11 to 42.26)	0.62
Diabetic papillitis	1 (0.0)	3 (0.0)	OR	0.94 (0.10 to 8.98)	0.95	0.90 (0.09 to 9.60)	0.93
Papilloedema	1 (0.0)	8 (0.0)	OR	2.50 (0.31 to 19.95)	0.39	6.50 (0.79 to 53.76)	0.083
Compressive optic neuropathy	0 (0.0)	11 (0.0)	OR	7.19 (0.37 to 138.88)	0.19	5.71 (0.26 to 126.24)	0.27
Congenital optic neuropathy	1 (0.0)	7 (0.0)	OR	2.16 (0.27 to 17.48)	0.47	1.70 (0.19 to 15.15)	0.64
Toxic optic neuropathy	1 (0.0)	7 (0.0)	OR	2.16 (0.27 to 17.48)	0.47	2.54 (0.25 to 25.34)	0.43
Radiation optic neuropathy	0 (0.0)	2 (0.0)	OR	1.58 (0.04 to 65.71)	0.81	1.08 (0.02 to 67.98)	0.97
Optic pallor or atrophy of unknown aetiology	3 (0.0)	13 (0.1)	OR	1.35 (0.39 to 4.74)	0.64	1.03 (0.27 to 3.91)	0.97
Traumatic optic neuropathy	1 (0.0)	9 (0.0)	OR	2.81 (0.36 to 22.15)	0.33	5.34 (0.23 to 126.31)	0.30

Logistic regression model. Values of p<0.0043 are considered statistically significant after applying a Bonferroni correction for multiple testing.
N/A, not available; NAION, non-arteritic anterior ischaemic optic neuropathy.

Table 3 Association between NAION and metabolic syndrome components

Association between NAION and	No NAION N (%), N=29 286	NAION N (%), N=99	Association measure	Unadjusted analysis		Adjusting for age, sex and race	
				Estimate (95% CI)	P value	Estimate (95% CI)	P value
Metabolic syndrome	22303 (76.2)	96 (97.0)	OR	10.02 (3.17 to 31.62)	<0.001	6.28 (1.96 to 20.14)	0.002
BMI ≥27 kg/m^2	18978 (64.8)	78 (78.8)	OR	2.02 (1.25 to 3.27)	0.004	1.84 (1.13 to 3.00)	0.014
Hypertriglyceridaemia	21516 (73.5)	95 (96.0)	OR	8.58 (3.15 to 23.33)	<0.001	5.63 (2.04 to 15.50)	<0.001
Hypoalphalipoproteinaemia	22109 (75.5)	96 (97.0)	OR	10.39 (3.29 to 32.79)	<0.001	6.86 (2.15 to 21.89)	0.001
Systemic hypertension	19381 (66.2)	87 (87.9)	OR	3.71 (2.03 to 6.78)	<0.001	2.19 (1.16 to 4.16)	0.016
Hyperglycaemia	18332 (62.6)	83 (83.8)	OR	3.10 (1.81 to 5.29)	<0.001	2.22 (1.28 to 3.86)	0.005
No of metabolic components							
0	2648 (9.0)	1 (1.0)		ref		ref	
1	2297 (7.8)	1 (1.0)	OR	1.15 (0.07 to 18.44)	0.92	0.98 (0.06 to 15.76)	0.99
2	2038 (7.0)	1 (1.0)	OR	1.30 (0.08 to 20.78)	0.85	0.97 (0.06 to 15.59)	0.98
3	5095 (17.4)	9 (9.1)	OR	4.68 (0.59 to 36.94)	0.14	3.17 (0.40 to 25.28)	0.28
4	7382 (25.2)	26 (26.3)	OR	9.33 (1.27 to 68.76)	0.029	5.42 (0.72 to 40.74)	0.1
5	9826 (33.6)	61 (61.6)	OR	16.44 (2.28 to 118.63)	0.006	8.58 (1.16 to 63.38)	0.035

Logistic regression model.
BMI, body mass index; NAION, non-arteritic anterior ischaemic optic neuropathy.

in MetS. MetS is a constellation of findings that portend a metabolic state with deleterious effects on overall health and longevity.[3–5 38] The presence of three or more of the following: obesity, systemic hypertension, insulin resistance, hypoalphalipoproteinaemia and hypertriglyceridaemia define MetS.[38] Excess calories and sedentary behaviour promotes visceral fat deposition, which in turn promotes lipid derangement and insulin resistance in susceptible individuals. Visceral fat deposition increases hepatic lipid flux, which in turn increases circulating triglycerides and HDL-cholesterol turnover[3 42] in patients with MetS. Furthermore, free-fatty acid excess and visceral adiposity promotes insulin resistance.[42 43] This cascade of events in susceptible individuals promotes endothelial dysfunction, atherogenesis and a chronic inflammatory state that likely leads to increased risk of pathologies including the acute hypoperfusion seen in NAION.

Each individual component of MetS has previously been associated with MetS: hypertension,[23 24 26–28] diabetes,[23 24 26 28–30] hypoalphalipoproteinaemia,[31 32] hypercholesterolaemia[23 28 29 33 34] and hypertriglyceridaemia.[28 33] Therefore, it is not surprising to find that MetS as a defined syndrome was also associated with NAION in our study. The question arises as to whether the individual components of MetS, or the distinct phenotype of MetS, are the key drivers of the association of NAION and MetS. Prior literature is difficult to interpret since many studies looking at the associations of components of MetS with a given phenotype do not specifically exclude patients if the complete MetS criteria are met.[12] It has been argued that MetS is greater than a sum of its parts being a truly altered state characterised by systemic markers of oxidative stress and inflammation that likely lead to the major sequelae of the disease.[44] Furthermore, each MetS component typically does not occur in isolation, and an abnormality in one often indicates systemic derangement, with abnormalities in the other components.[3] In our study, while we found a significant association between MetS and NAION, the data suggest that the key drivers in the association are hyperglycaemia, hypertriglyceridaemia and hypoalphalipoproteinaemia. Lipid derangements and insulin resistance indicators playing a significant role are in concordance with this pathophysiological explanation of MetS. Furthermore, the atherogenic and deleterious effects on microcirculation of hypoalphalipoproteinaemia,[40] hypercholesterolaemia[40 41] and hypertriglyceridaemia[45] significantly contributes to vascular disease. Abnormal lipid profiles cause endothelial dysfunction and is hypothesised to effect the microvasculature of the optic nerve, increasing susceptibility to perfusion defects and ischaemia.[28 33]

There are limitations to this study based on its retrospective nature including variation in documentation by providers. Our control population was one with normal eye exams other than the presence of cataract so we may have selected for a heathier overall population by excluding patients that have ocular manifestations of systemic disease. In addition, this was a population-based study reviewing patients in Olmsted, County, Minnesota, USA. Though state-specific MetS incidence data are lacking, Minnesota has similar rates

Table 4 Association between NAION and paired metabolic syndrome components

	Adjusting for paired metabolic component		Adjusting for paired metabolic component, age, sex and race	
Association between NAION and	**Estimate (95% CI)**	**P value**	**Estimate (95% CI)**	**P value**
BMI ≥27 kg/m^2	1.44 (0.88 to 2.34)	0.15	1.52 (0.93 to 2.48)	0.096
Hypertriglyceridaemia	7.64 (2.78 to 21.01)	<0.001	4.96 (1.79 to 13.77)	0.002
BMI ≥27 kg/m^2	1.42 (0.87 to 2.31)	0.16	1.50 (0.92 to 2.45)	0.11
Hypoalphalipoproteinaemia	9.20 (2.88 to 29.37)	<0.001	6.00 (1.86 to 19.32)	0.003
BMI ≥27 kg/m^2	1.59 (0.98 to 2.60)	0.062	1.68 (1.02 to 2.74)	0.040
Systemic hypertension	3.32 (1.80 to 6.13)	<0.001	1.94 (1.01 to 3.70)	0.045
BMI ≥27 kg/m^2	1.59 (0.97 to 2.61)	0.064	1.62 (0.99 to 2.66)	0.056
Hyperglycaemia	2.76 (1.60 to 4.78)	<0.001	1.99 (1.13 to 3.48)	0.016
Hypertriglyceridaemia	3.13 (0.79 to 12.47)	0.11	2.28 (0.54 to 9.71)	0.26
Hypoalphalipoproteinaemia	3.95 (0.81 to 19.28)	0.090	3.39 (0.65 to 17.84)	0.15
Hypertriglyceridaemia	6.26 (2.27 to 17.29)	<0.001	4.95 (1.78 to 13.75)	0.002
Systemic hypertension	2.51 (1.36 to 4.63)	0.003	1.69 (0.89 to 3.20)	0.11
Hypertriglyceridaemia	6.64 (2.41 to 18.28)	<0.001	4.88 (1.76 to 13.50)	0.002
Hyperglycaemia	2.22 (1.29 to 3.82)	0.004	1.84 (1.06 to 3.20)	0.029
Hypoalphalipoproteinaemia	7.45 (2.32 to 23.88)	<0.001	5.99 (1.86 to 19.29)	0.003
Systemic hypertension	2.49 (1.35 to 4.60)	0.003	1.66 (0.87 to 3.14)	0.12
Hypoalphalipoproteinaemia	7.94 (2.49 to 25.35)	<0.001	5.91 (1.84 to 18.94)	0.003
Hyperglycaemia	2.22 (1.29 to 3.81)	0.004	1.83 (1.06 to 3.17)	0.031
Systemic hypertension	2.87 (1.54 to 5.33)	<0.001	1.87 (0.98 to 3.57)	0.058
Hyperglycaemia	2.34 (1.35 to 4.06)	0.002	1.99 (1.14 to 3.48)	0.016
Metabolic syndrome	9.21 (2.83 to 30.00)	<0.001	5.31 (1.60 to 17.66)	0.006
BMI ≥27 kg/m^2	1.17 (0.71 to 1.92)	0.54	1.33 (0.81 to 2.20)	0.27
Metabolic syndrome	3.84 (0.98 to 15.14)	0.054	2.78 (0.69 to 11.24)	0.15
Hypertriglyceridemia	3.72 (1.13 to 12.26)	0.031	3.09 (0.92 to 10.36)	0.068
Metabolic syndrome	3.63 (0.91 to 14.48)	0.068	2.49 (0.60 to 10.25)	0.21
Hypoalphalipoproteinaemia	4.31 (1.08 to 17.17)	0.039	3.79 (0.93 to 15.48)	0.064
Metabolic syndrome	6.55 (1.97 to 21.77)	0.002	5.33 (1.59 to 17.83)	0.007
Systemic hypertension	2.07 (1.10 to 3.89)	0.024	1.39 (0.72 to 2.68)	0.32
Metabolic syndrome	7.10 (2.17 to 23.26)	0.001	4.98 (1.51 to 16.44)	0.008
Hyperglycaemia	1.87 (1.08 to 3.25)	0.027	1.62 (0.93 to 2.83)	0.092

BMI, body mass index; NAION, non-arteritic anterior ischaemic optic neuropathy.

of obesity to the USA average.[46] Nevertheless, it is difficult to know whether the conclusions reached from our study are applicable to the rest of the United States or worldwide. In addition, this population primarily self-identified as white, thus limiting generalisability to other populations. Also, the prevalence of MetS in our study was higher than prevalence rates in the USA, reported to be 46.7% in adults 60 years or older.[6] There may be a number of reasons for this highlighted by Wu *et al*,[21] most notably that population predisposed to have MetS components may have been selected for as only patients with available bloodwork were used. Furthermore, using BMI as an indicator of central adiposity could produce a population with an elevated MetS prevalence than that of the general population.[21] Not all optic neuropathies are mutually exclusive. For example, the presence of ODD is a risk factor for NAION[47] and, therefore, has potential to confound the results. In our study, two patients had both ODD and NAION. In a study of long-term metabolic stress to individuals, one would expect an association only with MetS and acquired conditions. However, we elected to include a comprehensive list of neuropathies including congenital optic neuropathy. Consistent with our hypothesis, there was no association with MetS and congenital optic neuropathy.

CONCLUSION

MetS was associated with NAION. For patients with NAION, though each individual component of MetS was individually associated, the strongest associations were with hypertriglyceridaemia, hypoalphalipoproteinaemia and hyperglycaemia. Further study is needed to determine whether MetS represents a modifiable risk factor for the development of NAION.

Contributors DK: data collection, analysis and interpretation of results, preparation of manuscript, final approval of manuscript KW: data collection, editing of manuscript, final approval of manuscript. LW: analysis and interpretation of results, editing of manuscript, final approval of manuscript. DH: analysis and interpretation of results, editing of manuscript, final approval of manuscript. JC: analysis and interpretation of results, editing of manuscript, final approval of manuscript. GR: study conception and design, analysis and interpretation of results, editing of manuscript, final approval of manuscript. GR is responsible for the overall content of the maniscript.

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Ethics approval The protocol for this study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. Data were stored and transferred in accordance with the Health Insurance Portability and Accountability Act of 1966 and the Declaration of Helsinki.

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Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

ORCID iD

Gavin W Roddy http://orcid.org/0000-0002-8905-8588

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