Acta Ophthalmologica

Metabolic syndrome and some of its components in relation to risk of cataract extraction. A prospective cohort study of men

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ABSTRACT.
Purpose: **To evaluate the relationship between metabolic syndrome and some of its components with the incidence of cataract extraction.**
Methods: **A population-based prospective cohort with a total of 45 049 men, aged 45–79 years, from the Cohort of Swedish Men completed in 1997 a self-administered questionnaire concerning anthropometric measurements and life-style factors. The men were followed from 1 January 1998 through 31 December 2012, and the cohort was matched with registers of cataract extraction. The main outcome measure was incident cases of age-related cataract extraction.**
Results: **Over the 15-years of follow-up, 7573 incident cases of cataract extraction were identified. After controlling for potential confounders, the association between single components of metabolic syndrome, abdominal adiposity, diabetes and hypertension and risk of cataract extraction was rate ratio (RR): 1.04; 95% confidence interval (CI): 0.99–1.10, RR: 1.77; 95% CI: 1.64–1.92 and RR: 1.06; 95% CI 1.00–1.13, respectively. The risk of cataract extraction increased with increasing numbers of metabolic syndrome components ($p < 0.0001$). Men aged 65 years or younger at baseline with all three components of the metabolic syndrome had a relative risk of 2.43 (95% CI: 1.95–3.01) for cataract extraction.**
Conclusion: **In this cohort of middle-aged and elderly men, metabolic syndrome with the combination of abdominal adiposity, diabetes and hypertension was associated with an increased risk for cataract extraction, especially among men aged 65 years or younger. These findings put emphasis on the importance of weight control and healthy lifestyle behaviours in order to prevent cataract.**

Key words: cataract – cohort studies – metabolic syndrome – risk factors

There is no conflict of interest and the authors had no financial disclosures

Acta Ophthalmol. 2019: 97: 409–414

doi: 10.1111/aos.13929

Introduction

Obesity is increasing worldwide. According to the World Health Organization (WHO), the prevalence of obesity has nearly tripled since 1975, and almost 40% of the adult global population are now overweight and 13% are obese (World Health Organisation 2015). Parallel with increasing obesity, the prevalence of diabetes (Guariguata et al. 2014) and hypertension (Kearney et al. 2005) is also rising.

The Metabolic syndrome (METS) is a cluster of metabolic risk factors for cardiovascular disease (CVD) and type 2 diabetes, which include obesity (particular abdominal adiposity), elevated blood glucose, high blood pressure and dyslipidemia (Alberti et al. 2009). METS has become a clinical and public health problem and is also associated with cancer as well as ocular diseases such as glaucoma (Newman-Casey et al. 2011) and retinopathy (Chopra et al. 2012). Limited data exist on the association of METS with cataract, the leading cause of blindness in the world.

Only three prospective studies have examined the association between METS and cataract and/or cataract extraction (Lindblad et al. 2008; Tan et al. 2008; Ghaem Maralani et al. 2013).

We previously examined, in a prospective cohort among middle-aged and elderly women, the association between METS and some of its components with risk of cataract extraction (Lindblad et al. 2008). Both METS and its single components such as abdominal adiposity, diabetes and hypertension were associated with increased risk of cataract extraction especially among women aged 65 years or less.

Lifestyle behaviour and prevalence of diseases may differ between men and women. In this prospective cohort study, we therefore intended to examine the association between METS and the components abdominal adiposity, diabetes and hypertension with risk of cataract extraction among middle-aged and elderly men.

Materials and Methods

The Cohort of Swedish Men

The Cohort of Swedish Men (COSM) was established in late autumn 1997, among men living in two counties in central Sweden, in order to prospectively study the association between different lifestyle factors and major chronic diseases, where cataract was included. All men aged 45–79 years received by mail a self-administered questionnaire concerning anthropometric measurements and lifestyle factors. The questionnaire included among others, questions about waist circumference, diagnoses of diabetes and hypertension, weight and height. Answers were obtained from 48 645 men (48.5%) who well represents the population of middle-aged and elderly men in Sweden (Lindblad et al. 2014). We excluded men who sent in blank questionnaires ($n = 92$), men with a diagnosis of cancer (other than non-melanoma skin cancer) before 1997 ($n = 2592$) or who died before baseline ($n = 55$). From the analysis, we excluded 857 men with cataract extraction before start of follow-up in 1998. The final study cohort included 45 049 men at start of follow-up for cataract extractions in January 1998.

The study was approved by the Regional Ethical Review Board at Karolinska Institutet (Stockholm, Sweden) and adhered to the tenets of the Declaration of Helsinki. Completion of the self-administered questionnaire was considered to imply informed consent.

Assessment and definition of metabolic syndrome components

We defined metabolic syndrome according to the Joint Scientific Statement, approved 2009 by several major organizations among them the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity in order to unify the criteria for the metabolic syndrome (Alberti et al. 2009). According to these recommendations, the presence of any three of the following five risk factors constitutes the metabolic syndrome; ethnic-specific elevated waist circumference, treatment for or elevated triglycerides or reduced high-density lipoprotein (HDL) cholesterol, elevated fasting glucose or drug treatment of elevated glucose, and elevated blood pressure or antihypertensive drug treatment. We used waist ≥94 cm as cut-off point of abdominal obesity for European men. As we had no information on triglyceride levels or HDL cholesterol in our study, we focused on central adiposity, diabetes and hypertension.

In this study, abdominal adiposity was estimated from self-reported waist circumference values at baseline. Validity of self-reported waist circumference has been reported to be high (Spearman $r = 0.80$) (Spencer et al. 2004). Current weight and height were obtained from the questionnaire. High validity has also been observed for self-reported height ($r = 0.91$) and weight ($r = 0.87$) compared with actual measurements among Swedish men (Kuskowska-Wolk et al. 1992). Body mass index (BMI) (kg/m^2) as an expression for overall obesity was estimated from self-reported weight and height. Information on hypertension was obtained from self-report in the questionnaire, and diagnoses of diabetes were obtained by linkage of the cohort to the National Patient Register and the National Diabetes Register as well as from self-report in the questionnaire.

Other exposures

From the questionnaire, we collected information on possible risk factors for cataract, including cigarette smoking (number of cigarettes smoked per day during several periods in life), alcohol consumption (frequencies and amounts of different beverages) use of corticosteroid medication, use of vitamin supplements, educational level and total physical activity.

Identification of incident cases and follow-up of the cohort

Using personal identification numbers, we matched the cohort against computerized registers of cataract extraction in the study area and with the Swedish National Cataract Register, which covers 96% of all cataract extractions in Sweden. We used the International Classification of Diseases, 10th Revision (ICD 10), code H25 for age-related cataract. Cataracts considered to be congenital, secondary to ocular trauma or intraocular inflammation and previous intraocular surgery (ICD10, code H26) were not included in the matching.

The cohort was followed until the date of cataract extraction, date of death or the end of the follow-up period (31 December 2012), whichever came first.

The dates of deaths in the cohort were ascertained from the Swedish Death Register which is 100 percent complete.

Statistical analysis

We estimated relative risks as rate ratios (RRs) with 95% confidence intervals (CI), by Cox proportional hazards regression models, using SAS (version 9.3; SAS Institute, Inc, Cary, NC, USA).

Relative risks were estimated for single components of the metabolic syndrome such as waist circumference, history of diabetes and hypertension, and for the metabolic syndrome (waist ≥94 cm for European men, diabetes and hypertension). Overall obesity measured as BMI (kg/m^2) was categorized into five categories based on the WHO guidelines, underweight (BMI < 18.5), normal weight (BMI: 18.5–24.9), overweight (BMI: 25–29.9), obese I (BMI: 30–34.9) and obese II (BMI ≥ 35), and relative risks were estimated for categories of current BMI. In multivariate analysis, we adjusted for other potential risk factors, including age (5-year age groups as incidence of cataract extraction with age is not linear; 45–49, 50–54, 55–59, 60–64, 65–69, 70–74 and 75–79 years), smoking (number of cigarettes smoked per day during several periods in life, converted into mean number of cigarettes smoked per day and divided into, never, past and current ≤10, >10 cigarettes/day), alcohol consumption (frequencies and amount of different beverages, converted into grams of alcohol and divided into quartiles), use of corticosteroid medication (yes/no), use of vitamin supplement/yes/no), educational level (<10, 10–12, >12 years) and total physical activity (metabolic equivalent of the task (MET)hours/day, divided into quartiles, with the sum of different types of activities defined as multiples of MET (kcal/kg/hr) multiplied by self-reported duration in hours for each activity). We stratified for age, using ≤65/>65 years as cut-off point, as BMI in our cohort started to decline from age of 65 years. All reported p values are two-sided, and $p < 0.05$ was considered statistically significant.

Results

We identified 7573 incident cases of cataract extraction during the study period 1 January 1998 through 1 December 2012. Almost 60% of the men in the cohort had signs of abdominal adiposity, with waist circumference more or equal to 94 cm and 26% had a waist circumference of more than 102 cm (cut-off point for obesity in the WHO guidelines). The prevalence of diabetes and hypertension in the cohort was 7% and 22%, respectively. Men with metabolic syndrome had a higher alcohol consumption, used less vitamin supplement, had a lower educational level and had a lower physical activity compared with men without metabolic syndrome. Other baseline characteristics are presented in Table 1.

The association between the metabolic syndrome and some of its components simultaneously adjusted for each other and risk of cataract extraction is shown in Table 2. The multivariate-adjusted relative risk for cataract extraction among men with waist circumference ≥94 cm was 1.04 (95% CI: 0.99–1.10), and among men with abdominal adiposity (waist > 102 cm), the relative risk was 1.08 (95% CI: 1.02–1.15).

There was a significant increased risk of cataract extraction with increasing number of components of the metabolic syndrome ($p < 0.0001$) (Table 3). Men with all three components of the metabolic syndrome (waist circumference ≥94 cm, diabetes and hypertension) had a twofold increased risk of cataract extraction (RR 2.04; 95% CI: 1.79–2.32) compared with men without any of these components (Table 3). Among men aged 65 years or younger, the relative risk was 2.43 (95% CI: 1.95–3.01).

In our analyses, we found no overall association between BMI and risk of cataract extraction. Only among men

Table 1. Baseline characteristics of the Cohort of Swedish Men 1997* by metabolic syndrome and its components.

		Waist ≥ 94 cm			Hypertension			Diabetes			Metabolic syndrome		
		No	Yes	p	No	Yes	p	No	Yes	p	No	Yes	p†
No. of men	*n*	15 014	21 290		34 907	10 142		41 830	3219		12 358	880	
Cataract extractions	*n*	2319	3916		5483	2090		6656	917		1759	270	
Age (years)	mean	59	61	<0.0001	59	63	<0.0001	60	64	<0.0001	59	65	<0.0001
Never smoker	%	34.9	37.5	<0.0001	34.8	37.2	0.0003	33.5	32.5	0.0016	41.9	34.7	<0.0001
Smokes 1-10 cig/day	%	6.9	8.1	<0.0001	6.7	8.0	<0.0001	6.2	6.1	0.0012	9.0	4.0	<0.0001
Smokes >10 cig/day	%	14.5	15.8	0.04598	15.5	15.5	0.06811	18.2	17.6	0.0042	14.8	13.0	0.4965
Ex smoker	%	43.6	38.6	<0.0001	43.1	39.4	<0.0001	42.1	40.8	0.0013	34.3	48.3	<0.0001
Alcohol consumption, g/day	Mean	13.9	15.9	<0.0001	14.8	16.3	<0.0001	15.2	14.5	0.03260	13.9	16.4	<0.0001
Steroid use	%	9.0	10.1	0.0011	9.1	11.4	<0.0001	9.5	11.6	0.0022	8.7	13.7	<0.0001
Vitamin supplement use	%	33.7	30.0	<0.0001	30.6	30.8	0.8929	30.7	29.8	0.0307	33.6	27.1	.0003
BMI, kg/m^2	Mean	23.5	27.3	<0.0001	25.4	27.1	<0.0001	25.7	27.4	<0.0001	23.4	29.5	<0.0001
Educational level, > 12 years	%	18.5	14.7	<0.0001	17.0	13.3	<0.0001	16.5	12.8	<0.0001	18.9	11.6	<0.0001
Physical activity, MET hr/day	Mean	42.2	41.2	<0.0001	41.7	41.1	<0.0001	41.6	41.0	<0.0001	42.3	40.4	<0.0001

BMI = body mass index, MET = metabolic equivalent of the task.
* All values (except age) are standardized to the age distribution in the study population.
† p-values are obtained *t*-test.

Table 2. Relative risk and 95% CI for cataract extraction by components of the metabolic syndrome and by age at baseline in the Cohort of Swedish Men 1997.

	RR (95% CI) Adjusted for age	RR (95% CI)* Multivariate model
Components of the metabolic syndrome		
Waist circumference ≥94 cm[b]		
All ages (*n* = 3916)	1.10 (1.0–1.16)	1.04 (0.99–1.10)
≤65 years (*n* = 1494)	1.11 (1.02–1.20)	1.05 (0.96–1.14)
>65 years (*n* = 2422)	1.09 (1.02–1.17)	1.04 (0.97–1.11)
Diabetes		
All ages (*n* = 917)	1.82 (1.70–1.95)	1.77 (1.64–1.92)
≤65 years (*n* = 346)	2.23 (1.99–2.49)	2.07 (1.82–2.37)
>65 years (*n* = 571)	1.63 (1.50–1.78)	1.64 (1.48–1.81)
Hypertension		
All ages (*n* = 2090)	1.17 (1.11–1.23)	1.06 (1.00–1.13)
≤65 years (n = 766)	1.29 (1.19–1.40)	1.17 (1.07–1.29)
>65 years (*n* = 1324)	1.10 (1.03–1.17)	1.00 (0.93–1.07)
All 3 components of the metabolic syndrome[‡] waist ≥ 94 cm[†] diabetes, and hypertension		
All ages (*n* = 270)	2.09 (1.84–2.38)	2.04 (1.79–2.32)
≤65 years (*n* = 94)	2.45 (1.98–3.04)	2.43 (1.95–3.01)
>65 years (*n* = 176)	1.92 (1.63–2.25)	1.84 (1.57–2.17)

CI = confidence interval; RR = rate ratio.
* Adjusted for age (5-year age groups; 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79), smoking (never, past, current ≤10, >10 cigarettes/day), alcohol consumption (g/day in quartiles), steroid medication use (yes/no), vitamin supplement use (yes/no), educational level (<10, 10–12, >12 years), physical activity (metabolic equivalent of the task, hr/day in quartiles).
[†] Waist cut-off point for European men according to Joint Interim Statement (JIS)[4].
[‡] Reference group is men without any of the three components of the metabolic syndrome.

Table 3. Relative risk and 95% CI for cataract extraction according to the number of components of the metabolic syndrome at baseline in the Cohort of Swedish Men 1997.

	RR (95% CI) Adjusted for age	RR (95% CI)* Multivariate model
Components of the metabolic syndrome		
None (*n* = 1759)	1.00	1.00
One of three (*n* = 2883)	1.09 (1.03–1.16)	1.07 (1.01–1.14)
Two of three (*n* = 1323)	1.25 (1.17–1.35)	1.22 (1.14–1.32)
All three (*n* = 270)	2.09 (1.84–2.38)	2.04 (1.79–2.32)
p for trend	<0.0001	<0.0001

CI = confidence interval; RR = rate ratio.
* Adjusted for age (5-year age groups; 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79), smoking (never, past, current ≤10, >10 cigarettes/day), alcohol consumption (g/day in quartiles), steroid medication use (yes/no), vitamin supplement use (yes/no), educational level (<10, 10–12, >12 years), physical activity (metabolic equivalent of the task, hr/day in quartiles).

with BMI ≥ 35 kg/m^2, a statistically significant association with cataract extraction was observed (RR: 1.39; 95% CI: 1.15–1.68) compared with men with normal BMI.

Discussion

This large population-based prospective cohort study, among middle-aged and elderly men, confirms that metabolic syndrome is positively associated with increased risk of cataract extraction, especially among men aged 65 years or younger. Our results are consistent with our previous prospective cohort study among middle-aged and elderly women in Sweden on the association between METS and cataract extraction (Lindblad et al. 2008). Two previous cross-sectional studies, one from Korea (Park et al. 2014) and one from Lithuania (Paunksnis et al. 2007) reported a significant association between METS and cataract among women but not among men.

Our finding of an increased risk of cataract with increasing number of METS components complies with previous cohort (Lindblad et al. 2008), cross-sectional (Sabanayagam et al. 2011; Park et al. 2014) and case–control studies (Galeone et al. 2010) both in the Western World (Lindblad et al. 2008; Galeone et al. 2010) and in Asia (Sabanayagam et al. 2011; Park et al. 2014).

Oxidative stress and an inflammatory mechanism are likely to contribute to the association between METS and cataract. The aetiology of cataract is multifactorial, and oxidative stress is of importance (Vinson 2006). C reactive protein (CRP) and pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) have been associated with cataract development (Schaumberg et al. 1999; Klein et al. 2006). Oxidative stress has also been associated with METS (Ando & Fujita 2009), and each component of METS has been associated with increased levels of CRP and cytokines (Bautista et al. 2005; Santos et al. 2005; Pou et al. 2007; Wang et al. 2013). A linear association with rising levels of CRP with increasing number of components of the metabolic syndrome (Ridker et al. 2003; Santos et al. 2005) is in concordance with a greater risk of cataract with increasing number of METS components.

We observed a weak positive association with central adiposity and cataract extraction. Central obesity has been related to cataract among cohort (Schaumberg et al. 2000; Jacques et al. 2003; Lindblad et al. 2008), cross-sectional (Leske et al. 1999; Paunksnis et al. 2007) and case–control studies (Galeone et al. 2010).

Obesity, especially abdominal adiposity is associated with a chronic low-grade state of inflammation (Santos et al. 2005). Among 1250 participants from the Framingham Heart Study, visceral adipose tissue was significantly related to CRP, IL-6 and TNF-α as well as with urinary isoprostanes, a marker of oxidative stress (Pou et al. 2007). An inflammatory mechanism connecting abdominal adiposity with cataract is supported by the findings from a nested case–control study within the Swedish mammography cohort where increased urinary levels of the isoprostane $PGF_{2\alpha}$ were associated with increased risk of cataract extraction (Selin et al. 2014).

Diabetes is viewed as a risk factor for cataract. Our finding of an association between diabetes and cataract extraction is consistent with findings from cohort (Klein et al. 1998; Jacques et al. 2003; Lindblad et al. 2008; Tan et al. 2008; Ghaem Maralani et al. 2013), cross-sectional (Leske et al. 1999; Sabanayagam et al. 2011; Richter et al. 2012; Park et al. 2014) and case–control studies (Galeone et al. 2010). Glucose uptake in the lens is an insulin-independent process. A hyperosmotic effect in the lens may contribute to cataract development by activation of the polyol pathway where aldose reductase catalyses reduction of glucose to sorbitol. Accumulation of sorbitol leads to an osmotic gradient with infusion of fluid and swelling and rupture of the lens fibres (Kinoshita et al. 1979). Nonenzymatic glycation occurs during normal ageing of the lens where glucose reacts with amino groups on proteins and leads to formation and accumulation of advanced glycation end products (AGE) in the lens (Singh et al. 2014). Glycation has been found to occur at a higher degree in diabetic lenses. Interaction of AGE with cellular receptors (RAGE) also generates pro-inflammatory cytokines such as interleukin-1 α (IL-1 α), IL-6 and TNF-α, indicating an inflammatory mechanism linking diabetes with cataract (Wang et al. 2013).

We observed a significant positive association between hypertension and cataract extraction. Previous cohort (Schaumberg et al. 2001; Lindblad et al. 2008; Tan et al. 2008), cross-sectional (Leske et al. 1999; Paunksnis et al. 2007; Sabanayagam et al. 2011; Richter et al. 2012) and case–control studies (Galeone et al. 2010) have reported an association between hypertension and cataract, but results are inconsistent (Klein et al. 1998; Wang et al. 2009). An association between TNF-α, IL-6 (Bautista et al. 2005), CRP (Ridker et al. 2003) and hypertension has been reported indicating an underlying inflammatory mechanism linking hypertension with cataract (Schaumberg et al. 1999; Klein et al. 2006). Antihypertensive medication has also been reported to be associated with cataract. The Blue Mountain Eye Study reported in a 10-year follow-up study an association between β- blockers and both nuclear cataract and cataract extraction, which biologically could be explained by disturbance in electrolyte balance in the lens fibres (Kanthan et al. 2009). An association between potassium-sparing diuretics and posterior subcapsular cataract was previously observed in the Beaver dam study (Klein et al. 2001), but the effect of anti-hypertension medication could be explained by confounding by indication.

The strengths of our study include a population-based prospective design with information on possible risk factors before cataract extraction, which minimize the risk for recall bias; a large study size; information on potential confounders and a long follow-up which is almost complete.

There are, however, some potential limitations in our study. Misclassification of exposures may occur due to self-reported measurements of waist circumference, weight and height. A previous study among men and women in Sweden reported a tendency for high values to be underestimated and low values to be overestimated (Kuskowska-Wolk et al. 1992).

Some misclassification regarding history of diabetes and hypertension may also occur. However, we included information from several sources completing each other, as the National Patient Register, the National Diabetes Register and from self-reports in the questionnaire. The prevalence of diabetes and hypertension in the cohort was in concordance with the prevalence among Swedish men in the same age group and time period (Statistics Sweden (SCB)). The prevalence of abdominal adiposity (>102 cm), diabetes and hypertension among men aged 60 in the study cohort was also similar to the prevalence among Swedish men in the same age group and time period in a Swedish study by Halldin et al. (Halldin et al. 2007); 23,0%, 7,3% and 23,8% versus 27,6%, 8,1% and 17,9%, respectively. Potential misclassification of anthropometric factors, diabetes and hypertension is, due to the prospective design of the study, likely to be similar for men who developed cataract and men who did not, which would weaken the observed association.

We had no information on triglyceride levels or HDL cholesterol and, therefore, had an underestimation of the metabolic syndrome which would attenuate the risk estimates.

Information on cataract subtype was not available. As lens opacity is clinically relevant only if visual function has declined considerably, we focused on the degree of cataract severe enough to affect activities of daily life, thus requiring lens extraction and, therefore, of greatest clinical, economic and public health importance. The mean preoperative best-corrected visual acuity was, according to the Swedish National Cataract Register, 20/60 Snellen equivalents in the eye with cataract extraction compared with 20/32 Snellen equivalents in the unoperated eye during the study period.

There is a potential of bias as patients with diabetes are under regular ophthalmic care and, therefore, may have cataract extraction more easily. However, due to the Swedish healthcare system, all men in the study had the same access to cataract surgery with a patient fee less than $50 per operation. We cannot exclude a possibility for potential bias due to underestimation of cataract extraction, but this would lead to attenuation of the observed risk estimates (Rothman & Greenland 1998).

In this cohort of middle-aged and elderly men, metabolic syndrome with the combination of abdominal adiposity, diabetes and hypertension was associated with a more than twofold increased risk of cataract extraction, especially among men aged 65 years or younger. These findings give emphasis to the importance of weight control and healthy lifestyle changes in order to prevent cataract in a time when obesity and metabolic syndrome have become a worldwide problem.

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Received on March 24th, 2018.
Accepted on July 21st, 2018.

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This work was supported by research grants from Örebro County Council, Örebro, Sweden.
There is no conflict of interest and the authors had no financial disclosures