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Review

A systematic literature review of observational studies of the bidirectional association between metabolic syndrome and migraine

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ABSTRACT

Aims. – To evaluate all epidemiological evidence in the literature linking the metabolic syndrome (MetS) and migraine in adults.
Methods. – Database (Medline, Embase; published reports up to November 2017) and manual searches were performed. Information on data collection, sample characteristics, study design, MetS and migraine assessment, and results was extracted from each relevant publication. The methodological quality of each study was also assessed.
Results. – A total of 15 observational epidemiological studies in adults, published between 2009 and 2017, were retrieved. Of these, one employed a prospective design, while the rest had a cross-sectional (13 studies) or case–control (one study) design. Five studies assessed the presence of migraine in individuals with MetS, whereas 10 studies assessed the presence or risk of MetS in migraineurs. Most participants were female hospital outpatients. The sole prospective cohort study reported 11-year MetS incidence of 21.8% in migraineurs with aura, 16.8% in migraineurs without aura and 14.5% in subjects without headaches. Most studies (60%) provided no statistical estimates of association. Methodological flaws included selection biases, lack of power analysis, unsuitable research plans and no multivariable analyses. Meta-analysis was not feasible with the available data.
Conclusion. – Our systematic review has identified major gaps in knowledge and weaknesses in research that should provide an impetus for future epidemiological investigations using more rigorous methodology, large general-population prospective cohorts, and substantial data on dietary behaviours and lifestyle.

Introduction

The Global Burden of Disease Study 2015 [1] placed migraine as the seventh leading cause of years lived with disability. This is a primary headache disorder with unilateral, recurring attacks of moderate-to-severe pain intensity and concurrent photophobia, phonophobia and nausea [2,3]. In pathophysiological terms, two distinct disorders—migraine without aura and migraine with aura—are known [4]. The aura most likely has a cerebral cortical origin [5], so migraine with aura is characterized by visual, sensory or other central nervous system symptoms that usually develop gradually and precede migraine attacks [3]. The prevalence of migraine shows notable variation by region, although headache disorders in general are underestimated all over the world [2]. Migraine has been associated with an increased risk of cardiovascular disease, psychiatric and neurological disorders, and obesity [6,7]. Moreover, in some individuals, migraine undergoes clinical transformation from an episodic (≤ 14 days of headache/month) to a chronic (≥ 15 days of headache/month) state, underpinned by alterations in nociceptive thresholds and pain pathways and, occasionally, the emergence of brain lesions [5,8]. Individuals with chronic migraine and those suffering from migraine with aura appear more likely to experience comorbidities (depression, hypertension, diabetes, obesity, respiratory disorders) compared with their counterparts with episodic migraine or migraine without aura [9–11].

Long-term migraine and increased attack frequencies have been associated with cardiometabolic characteristics of migraineurs, such as higher Framingham risk scores, dyslipidaemia,

Abbreviations: CI, confidence interval; MeSH, Medical subject headings; MetS, metabolic syndrome; NIH, National Institutes of Health; OR, odds ratio.

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insulin resistance and obesity, all of which are features of the metabolic syndrome (MetS) [12–14]. Indeed, pharmacological treatment of migraine may include medications stimulating weight gain, hypertension and/or dyslipidaemia [15–17]. Conversely, MetS (and obesity in particular) has been suggested as a risk factor for migraine progression possibly via inflammatory and immune-system mediators [9,16,18]. MetS – an established predictor of diabetes, atherosclerosis and cardiovascular disease [19]—is considered present when three or more of the following criteria are met: abdominal obesity (waist circumference ≥ 94 cm for men, ≥ 80 cm for women, although other cut-offs may also be used); hypertension (systolic/diastolic blood pressure ≥ 130/85 mmHg and/or use of antihypertensive treatment); raised triglycerides (≥ 1.7 mmol/L or medication use); low high-density lipoprotein (HDL) cholesterol (< 1.00 mmol/L for men, < 1.30 mmol/L for women); and raised fasting glucose levels (≥ 5.6 mmol/L and/or use of antidiabetic treatment) [20]. The prevalence of each MetS component, the cut-off values and, thus, MetS overall vary across regions [20–22]. For example, using aggregated 2003–2012 data, the prevalence of MetS in the US was estimated at 33% [21].

Yet, given the current knowledge, it remains unclear whether migraine is more likely to act as a progressive trigger of MetS or vice versa. It is likewise unconfirmed whether the MetS–migraine association consistently varies by type of migraine (chronic, episodic, with or without aura) and/or by age and gender. The prevalence of migraine is most likely highest before age 45, and is twice as common in women than in men [2]. Conversely, the prevalence of MetS increases with age and is highest after age 60 [21]. With the present systematic review, the aim was to evaluate the epidemiological evidence linking these two disorders to provide a comprehensive understanding of their association, identify any consistent moderating factors and outline the direction of future investigations.

Methods

Our intention was to synthesize data from all observational epidemiological studies with a bearing on the link between MetS and migraine in adults. An extensive search was therefore performed of Embase and Medline/PubMed (all available reports from the beginning of database indexing up to November 2017), supplemented by a manual search through the reference lists of retrieved articles. Published conference proceeding abstracts were also considered. No language restrictions were applied. MeSH indexing terms “metabolic syndrome X” and “abdominal obesity metabolic syndrome” were associated with “migraine disorders”, “migraine without aura”, “migraine with aura”, “headache”, “headache disorders, primary” and “headache disorders”. A total of 253 and 17 articles were identified from database and manual searches, respectively. From the pool of non-duplicated hits, all review articles (with no original data) and research reporting on individual MetS components, but not MetS itself, were excluded. Ultimately, a total of 15 studies met the selection criteria (Fig. 1) and were subjected to detailed reviews performed independently by two investigators (V.A.A. and E.K.-G.). From each study, the following information was extracted: place and year of data collection; type and size of sample; study design; MetS and migraine assessment criteria; migraine treatment; and results [prevalence, incidence, odds ratio (OR) or other estimates of association, statistical adjustment]. In our summary of findings, the term “presence” was employed when referring to estimates obtained from cross-sectional and case-control (retrospective)

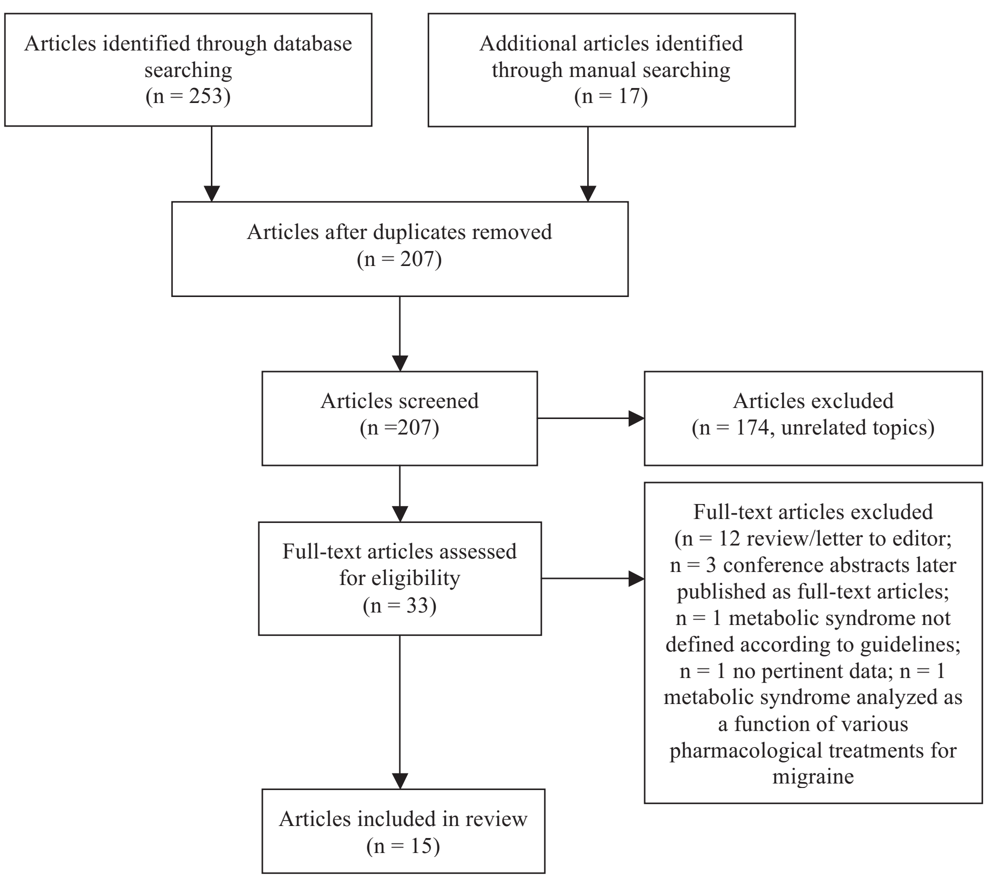

Fig. 1. Flow diagram of study selection for the present literature review.

studies, and the term "risk" was used when referring to estimates obtained from prospective studies.

Also assessed was the methodological rigour of each selected study, according to a US National Institutes of Health (NIH)-derived quality-assessment tool [23]. Owing to the lack of statistical estimates of association in most of the reviewed studies and the heterogeneity of the reference categories (in studies providing such estimates), meta-analysis of the available data was not feasible. Because this systematic review was based exclusively on publicly available published literature, it was exempt from ethics committee review. However, the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Checklist [24] was completed.

Results

Settings, study samples and definitions

Our summarized findings are presented in Table 1. Of the 15 reviewed studies (all English language, published between 2009 and 2017), only one employed a prospective design, whereas the rest had a cross-sectional (13 studies) or case-control (one study) design. The research came from countries in Europe, North and South America, Asia and Middle East. Although most study samples (73%) comprised female hospital outpatients, there was a substantial diversity in reference (comparison) groups owing to wide disparities in inclusion criteria.

Given that different MetS guidelines have been advanced [20,25,26], most studies employed those that were current at the time of the research. The principal difference among the various MetS definitions was whether or not central obesity is an obligatory component with agreed-upon cut-offs [20]. In general, larger waist circumference thresholds were used in North America than in the rest of the world [20]. In turn, the definition of migraine followed International Headache Society criteria in 11 studies (73%), half of which also assessed the severity of migraine via a visual analogue scale [27]. Migraine treatment was inconsistently reported; three studies specifically excluded regular users of antimigraine drugs [17,28,29]; one study included only participants taking chronic migraine treatment [30].

Presence of migraine in subjects with MetS

Five studies (33%) dealt with the presence of migraine (dependent variable) in subjects with MetS (independent variable). Sample sizes ranged from 60 to 980 individuals with MetS, while mean ages ranged from 40.8 to 54.4 years. All five studies employed cross-sectional analyses. The presence of migraine in those with MetS also varied greatly (from 2.8% to 58.3%), with marked disparities regarding reference groups. Only one of the five studies reported a statistical estimate of association, with a non-significant OR of 1.18 (95% CI: 0.72–1.92) adjusted for age and gender [31]. Two studies evoked gender-specific differences, with MetS females being more likely to report migraine (overall or episodic) than were MetS males [32,33].

Presence (or risk) of MetS in subjects with migraine

Regarding MetS (dependent variable) in individuals with migraine (independent variable), eight studies employed cross-sectional analyses, one study used a case–control design and another study assessed the incidence of MetS using a prospective design. Sample sizes ranged from 22 to 4411 migraineurs, with mean ages ranging from 31.4 to 50.0 years. In the cross-sectional studies, the presence of MetS in migraineurs ranged from 12% to 33%, with marked disparities among the reference groups. Three of the cross-sectional studies reported ORs. Specifically, a Brazilian study of current/former civil servants revealed a significant inverse association between MetS and definite migraine only among men (adjusted OR: 0.65, 95% CI: 0.43–0.99) [34], whereas positive associations were noted for chronic migraine in a Chinese study of female outpatients (adjusted OR: 5.34, 95% CI: 1.16–24.6) [17] and for migraine with aura in a Belgian general-population-based cohort (adjusted OR: 3.45, 95% CI: 1.63–7.29) [35]. However, disparities were observed in their multivariable adjustments.

A prospective general-population cohort in Norway revealed an 11-year incidence of MetS of 21.8% in migraineurs with aura, 16.8% in migraineurs without aura and 14.5% in those with no headaches [36]. Furthermore, significant effect modification by smoking status was observed, with adjusted incidence risk ratios for development of MetS of 2.10 (95% CI: 1.53–2.89) among migraineurs with aura who were smokers, 1.39 (95% CI: 1.03–1.86) among migraineurs with aura who were non-smokers, and 1.26 (95% CI: 1.12–1.42) in migraineurs without aura irrespective of smoking status [36].

Associations by aura status

The type of migraine as regards the presence of aura was inconsistently evaluated, and one study included only migraineurs without aura [37]. Of the studies evaluating the MetS–migraine association according to aura status, four of them reported non-significant findings [17,29,32,38]. Also, as noted above, the presence (and risk) of MetS was increased in migraineurs with aura compared with migraineurs without aura and non-migraineurs [35,36].

Associations with chronic migraine

Chronic and episodic migraine was not systematically distinguished, while one study included only those with chronic migraine [30]. As noted above, another study revealed a significant positive association between MetS and chronic migraine in female outpatients [17]. Finally, a non-significant adjusted OR of 0.88 (95% CI: 0.79–1.16) was reported for the association of MetS with either chronic or episodic migraine [39].

Study-quality assessment

Substantial variability was observed across studies regarding methodological rigour and quality (Table S1; see supplementary materials associated with this article online). While research objectives were often clearly stated, most studies proposed no specific hypotheses. Only one study performed a preliminary power analysis and sample-size calculation [32]. Other methodological deficiencies, identified by an NIH-derived quality-assessment tool for observational epidemiological studies, included a frequent lack of information on response rates, insufficient information on recruitment strategies, a strong potential for selection biases, use of unsuitable research plans (especially in studies reporting recruitment of control participants, yet performing cross-sectional analyses) and a frequent absence of multivariable analysis. In fact, nine of the 15 studies provided no statistical estimates of association [OR, relative risk].

Discussion

To the best of our knowledge, this is the first systematic review to address the quantity and quality of published epidemiological research on the association between MetS and migraine. Interest in this domain appears to be relatively recent, as all 15 reviewed studies were published between 2009 and 2017. Possibly driven by the greater prevalence of migraine in women than in men, the large

Table 1
Summary of observational epidemiological findings on the association between the metabolic syndrome (MetS) and migraine in adults.

Reference	Setting & period of data collection	Study design	Sample population	MetS assessment	Migraine assessment & treatment	Results			
						MetS with migraine (%)	Migraineurs with MetS (%)	OR (95% CI) or other risk estimate	Additional results
Presence of migraine in subjects with MetS									
Guldiken et al. (2009) [32]	Endocrinology & internal medicine outpatient clinics, Turkey; period n/a	Cross-sectional	210 subjects with MetS (72% female); ages 20–70; mean age 52.4 ± 9.9	ATP-III criteria	Clinical exam; ICHD-2 criteria (IHS); VAS; treatment n/a	19.5% (11.9% male, 22.5% female)	–	–	Diabetes, increased WC, BMI more frequent in migraineurs vs non-migraineurs; hypertension & dyslipidaemia NS; NS by presence of aura; attack frequency significantly associated only with BMI
Schultz et al. (2010) [31]	Workplace health screening, USA; 2004–2006	Prospective cohort (cross-sectional analysis for migraine)	3285 employees (17% female); MetS: 29.8% in 2004, 32.1% in 2006; mean age 40.8	AHA/NHLBI criteria	Self-reported diagnosis & treatment	2.8% (2.9% in those without MetS)	–	1.18 (0.72–1.92) adjusted for age, gender	NS association between MetS & migraine; role of migraine treatment n/a
Hamed et al. (2012) [28]	Diabetes outpatient clinic, Egypt, 2010–2011	Case–control (cross-sectional analysis)	60 subjects with MetS & headaches (93.3% migraine); ages 32–55; mean age 47.8 ± 7.3, 63% female; 40 matched controls (22.5% migraineurs)	2009 Joint Interim Statement criteria	Clinical exam; IHS criteria; excluding regular users of antimigraine, antidiabetic, antihypertensive or lipid- lowering drugs	58.3% EM; 35% CM	–	–	Comorbid migraine with MetS related to total & abdominal adiposity, insulin abnormalities
Gozke et al. (2013) [37]	Hospital outpatients, Turkey; period n/a	Cross-sectional	120 subjects with MetS (75% female); ages 29–84; mean age 54.4 ± 11.6	ATP-III criteria	Clinical exam; ICHD-2 criteria (IHS); VAS; analgestic drug use	15%	–	–	Hypertriglyceridaemia more common in migraineurs vs non-migraineurs; only migraineurs without aura; NS correlations between attack frequency & each MetS parameter; NS role of analgestic drug use
Demiryürek et al. (2016) [33]	Endocrinology outpatient clinic, Turkey; 2011–2012	Cross-sectional	202 (80.7% female); ages 20–70; mean age 49.9 ± 11.1	IDF criteria	Clinical exam; IHS criteria; VAS; analgesic drug use history & frequency	14.4% EM (14.7% females, 12.8% males); 8.4% EM + episodic tension-type headache (8.6% females, 7.7% males)	–	–	Significant correlation between triglyceride levels & attack frequency/ severity; role of migraine treatment n/a

Table 1 (*Continued*)

Reference	Setting & period of data collection	Study design	Sample population	MetS assessment	Migraine assessment & treatment	Results			
						MetS with migraine (%)	Migraineurs with MetS (%)	OR (95% CI) or other risk estimate	Additional results
Presence of MetS in subjects with migrai									
Anjum et al. (2009) [30]	University headache clinic, USA; period n/a	Cross-sectional	22 subjects treated for CM, ages 17–59, mean age 40.5; 73% female	n/a	Assessment n/a; treated with topiramate, nortriptyline, duloxetine, venlafaxine	–	13.6%	–	Evoked dyslipidaemia as principal MetS component in relation to migraine
Bhoi et al. (2012) [38]	Neurology outpatient service, India, 2009–2010	Cross-sectional	135 migraineurs (80% female); ages 14–61; mean age 31.4 ± 10.5	ATP-III, IDF criteria	Clinical exam; IHS criteria; treatment n/a	–	31.9%	–	MetS more common in elderly female migraineurs with multiple triggers, longer durations of headache; NS by presence of aura; NS by attack frequency
Winsvold et al. (2013) [36]	HUNT2 and HUNT3 general-population cohorts, Norway; 1995–2008	Prospective cohort; median follow-up 11.3 years	19,895 (age $\geq$ 20, median age $\sim$ 47 at baseline); 55% female; 1904 (9.6%) migraineurs	Modified ATP-III criteria	Self-reported questionnaire, interview; modified IHS criteria; treatment n/a	–	21.8% in migraineurs with aura; 16.8% in migraineurs without aura (vs 14.5% in subjects with no headache)	Migraine with aura: RR 2.10 (1.53–2.89 in smokers); 1.39 (1.03–1.86 in non-smokers); migraine without aura: RR 1.26 (1.12–1.42); adjusted for age	Migraine with aura associated with increased risk for developing MetS, with effect modification by smoking status; moderate risk increase for migraine without aura not modified by smoking
Fava et al. (2014) [39]	Hospital outpatient headache centre, Italy; 2011–2013	Case–control	83 CM subjects (mean age 41 ± 5.9), 83 EM subjects (mean age 40 ± 4.7); 83 matched healthy controls (100% female)	IDF criteria	Clinical exam; ICHD-3-beta criteria (IHS); treatment with NSAIDs, triptans, opiates	–	29% in CM, 26% in EM (vs 21% in controls; all $P < 0.01$)	AOR: 0.88 (0.79–1.16); $P = 0.34$ CM vs EM; adjusted for age, gender, drug use, BMI, WC, depression, hypertension, glycaemia, blood profile, Hb1Ac triglycerides	Higher presence of MetS in migraineurs vs controls; NS by EM/CM; significantly increased risk of insulin resistance, obesity in CM vs EM; triptans & NSAIDs significantly higher in CM vs EM
Salmasi et al. (2014) [49]	Neurology outpatient service, Iran; 2011–2013	Case–control (cross-sectional analysis)	200 migraineurs (mean age 34.3 ± 10.9); 200 matched healthy controls; overall 81% female	ATP-III criteria	Clinical exam; IHS criteria; VAS; treatment n/a	–	17% vs 15% in controls, $P > 0.58$	–	NS correlation between migraine & MetS; increased BMI, WC in migraineurs vs controls
Celikbilek et al. (2015) [29]	Neurology outpatient service, Turkey; period n/a	Case–control (cross-sectional analysis)	42 migraineurs (93% female); ages 18–50; median age 35; 40 matched controls	ATP-III criteria	Clinical exam; ICHD-2 criteria (IHS); VAS; without treatment	–	33% (vs 5% in controls; $P = 0.001$)	–	MetS more frequent in migraineurs vs controls; attack frequency lower in migraineurs with MetS vs no MetS; NS by presence of aura

Table 1 (*Continued*)

Reference	Setting & period of data collection	Study design	Sample population	MetS assessment	Migraine assessment & treatment	Results			
						MetS with migraine (%)	Migraineurs with MetS (%)	OR (95% CI) or other risk estimate	Additional results
Goulart et al. (2015) [34]	ELSA-Brasil cohort of civil servants, Brazil; 2008–2010	Cross-sectional	14,953 (4411 migraineurs; 76.2% female; mean age 50 ± 8.0); ages 35–74	ATP-III criteria	Self-reported questionnaire, IHS criteria; treatment by antiepileptics, beta-blockers, antidepressants	–	19.9% (vs 24.3% in non-migraineurs, $P < 0.05$)	OR 0.65 (0.43–0.99) in men; OR 0.88 (0.73–1.05) in women; adjusted for age, education, race, income, use of migraine prophylaxis drugs	Significant inverse association between MetS & definite migraine only in men; NS for probable migraine in either gender; positive association between migraine (definite, probable, overall) & dyslipidaemia only in women
He et al. (2015) [17]	Neurology outpatient service, China; 2013	Cross-sectional	142 migraineurs (females); ages 18–65; mean age 43.3 ± 8.3	ATP-III criteria	Questionnaire, clinical exam; ICHD-2 criteria (IHS); VAS; analgesic drug use; excluding those using regular prophylactic drugs for past 3 months	–	12%	OR 5.34 (1.16–24.6); $P = 0.03$; adjusted for age, residence, BMI, waist-to-height ratio, smoking, drinking history	Link between CM & MetS attenuated after adjustment for analgesic overuse; NS by presence of aura
Krongsut et al. (2016) [40]	Headache outpatient clinic, Thailand, 2015	Cross-sectional	162 adult migraineurs (87.2% female)	Self-reported during clinic visit, criteria n/a	Self-reported diagnosis & treatment during clinic visit, criteria n/a	–	18.5%	–	Male gender, migraine severity associated with MetS; association by presence/absence of aura n/a; NS by migraine frequency or type of treatment
Streel et al. (2017) [35]	NESCaV project, stratified random sample, Belgium; 2010–2012	Cross-sectional	731 with MetS data, 116 migraineurs without aura (15.3%, median age 39.4, 69.8% female); 79 migraineurs with aura (10.5%, median age 39.7, 59.5% female)	Revised ATP-III criteria	Self-reported ef-ID Migraine questionnaire; treatment n/a	–	28.1% in migraineurs with aura; 12.8% in migraineurs without aura; 19.1% in non-migraineurs	OR 3.45 (1.63–7.29) adjusted for age, gender, district, sedentariness, smoking, family history of myocardial infarction, stroke, hypertension	Migraineurs with aura at higher risk of MetS vs non-migraineurs; NS for migraine without aura

AHA/NHLBI: American Heart Association/National Heart, Lung, and Blood Institute; AOR: adjusted odds ratio; ATP-III: Adult Treatment Panel of Third National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults; BMI: body mass index; CM: chronic migraine; EM: episodic migraine; ICD-9-CM: International Classification of Diseases, 9th Revision–Clinical Modification; ICHD: International Classification of Headache Disorders; IDF: International Diabetes Federation; IHS: International Headache Society; n/a: not available or not reported; NESCaV: Nutrition, Environment and Cardiovascular Health; NS: not statistically significant ($P > 0.05$); NSAIDs: non-steroidal anti-inflammatory drugs; OR: odds ratio; RR: risk ratio (incidence); VAS: visual analogue scale; WC: waist circumference.

majority of research participants were women. Five studies addressed the presence of migraine in people with MetS, whereas the remaining 10 addressed the presence of MetS in those with migraine. However, marked disparities in inclusion/exclusion criteria highlighted important differences in reference groups, thereby reflecting negatively on the reliability of the current data on the MetS–migraine association, and precluding any inferences of MetS prevalence in people with migraine and vice versa. Even though a large majority of our reviewed studies included hospital outpatients, the specific selection criteria varied from none [40] to exclusion of subjects who were pregnant or had malignancies, or hepatic, renal or heart failure, diabetes, hyperlipidaemia, hypertension, thyroid disease, anaemia, morbid obesity, were smokers or consumed alcohol [29]. Age restrictions also varied from none [30] to 18–65 years [17] and 20–70 years [32]. Overall, participants were recruited from endocrinology/internal medicine/diabetes outpatient clinics, workplaces, headache/neurology clinics and the general population. Such considerations, coupled with the frequent absence of statistical estimates of association, precluded meta-analysis. However, meta-analyses of observational studies of the association between one MetS component (obesity, as assessed by body mass index) and migraine were feasible, revealing significant positive associations [41,42].

Some authors have indicated that migraine is associated with MetS incidence primarily among younger individuals whose cardiovascular risk is generally lower whereas, in their older counterparts, neurovascular changes, neuropathy and/or selective survival may obscure the link or even lead to seemingly protective effects [43]. Our present review, however, revealed no age-specific associations. Also, only one of our 15 studies reported that MetS was more common in elderly female migraineurs, with multiple triggers and longer durations of headache compared with their younger counterparts [38]. However, that study failed to perform any multivariable analyses. Even though the present review was focused on MetS in general, it was nevertheless clear that no individual MetS component emerged as significantly related to migraine in any consistent fashion.

Previous literature reports have documented that migraineurs with aura are at increased odds of having unfavourable cardiometabolic profiles, elevated Framingham risk scores [11,13] and comorbidities [10]. In the present review, two studies reported that the presence (and risk) of MetS was increased in migraineurs with aura compared with migraineurs without aura and non-migraineurs [35,36]. However, type of migraine as regards aura status was not systematically assessed, thereby making it not possible, given the paucity and limitations of the available data, to conclude whether the MetS-migraine association consistently varies by aura status. Migraines with and without aura are, in fact, distinct entities with disparate pathophysiologies and symptomatologies [3,4]. Likewise, the reviewed studies failed to systematically distinguish between chronic and episodic migraines. The former results from a series of clinical, physiological and anatomical transformations [5,8], and sufferers of chronic migraine, unlike their counterparts with episodic migraine, have an increased likelihood of experiencing physical and mental comorbidities such as hypertension, diabetes, obesity, respiratory disorders, depression and anxiety disorders [9]. The present review, in fact, found only one study showing a significant positive association between MetS and chronic migraine [17].

Most of our reviewed studies provided no statistical estimates of association, which was a major methodological flaw. In the studies reporting such estimates, multivariable adjustments varied from controlling for age and gender [31] to controlling for age, gender, residential district, sedentariness, smoking, and family history of myocardial infarction, stroke and hypertension [35,36]. In addition, only one of the studies employed formal interaction tests to reveal that the MetS–migraine association differed by smoking status [36]. Furthermore, only one of the studies revealed gender-specific statistical estimates of association, yet reported no formal interaction tests. Specifically, the presence of MetS was lower in men than in women [34]. Thus, consistent, statistically supported moderating factors of the MetS–migraine association could not be identified from the presently available data.

Although the side-effects of migraine treatment can include MetS components (weight gain, hypertension, dyslipidaemia) [15–17], in our reviewed studies, migraine treatment (and its role) was inconsistently reported. Apart from the side-effects of such pharmacological treatments, the association between MetS (and vascular disorders in general) and migraine has been addressed by previous research into underlying pathophysiological abnormalities, including inflammation, insulin resistance, hypothalamic and endothelial dysfunction, and high levels of leptin and orexin A [36,44–46]. Moreover, the association of migraine with some of these abnormalities has been shown to be amplified by obesity [39].

Methodological flaws of the reviewed studies included a frequent lack of information on response rates, no details on recruitment strategies, a strong potential for selection bias and use of unsuitable research plans. Only one of the 15 studies performed a preliminary power analysis and sample-size calculation [32]. Furthermore, only 47% (seven studies) dealt with the issue of prevention, mostly evoking weight loss and dietary modification as risk-reduction strategies. Of these, only one [31] addressed prevention in a comprehensive manner. In general, lifestyle-based strategies for prevention of these disorders include not only dietary modification and weight loss, but also stress management, sleep hygiene and physical activity (particularly in cases of MetS) [16], all of which can ameliorate the implicated pathophysiological abnormalities.

The currently rapidly rising rates of obesity and diabetes emphasize the importance of preventative action for both MetS and migraine [47,48]. The need for implementation of educational and screening programmes, and the involvement of employers, healthcare providers and public-health decision-makers have all been raised [31]. Yet, to our knowledge, this is the first study to evaluate, in a systematic manner, the quantity and quality of the published research pertaining to the association of MetS and migraine. In fact, our review has identified gaps in knowledge and weaknesses in research that should provide an impetus for future epidemiological investigations using more rigorous methodology, large general-population-based prospective cohorts, and substantial data on dietary behaviours and lifestyle.

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Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary materials (Table S1) associated with this article can be found at http://www.sciencedirect.com et https://doi.org/10.1016/j.diabet.2017.12.004.

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