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REVIEW

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Risk factors associated to disability in primary headaches: a systematic review to inform future iterations of the Global Burden of Disease Study

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Abstract

Background Headache disorders are prevalent and disabling conditions. Despite the recent introduction of modern therapies, a large portion of patients are still sub-optimally treated, resulting in a minor or no decrease in health loss nor disability. The Global Burden of Disease (GBD) study classifies 88 risk factors which impact several conditions, thus enabling the estimation of the potential health gain due to addressing these risk factors, but such analysis is not available for headache disorders yet.

Objective To address which risk factors, as intended by the taxonomy of the GBD study, are associated to disability in primary headaches.

Methods Primary research studies addressing primary headache disorders and disability were searched in PubMed, Web of Science and SCOPUS, in the period between 2000 and 2025. The GBD taxonomy, which classifies risk factors into environmental and occupational, behavioural, and metabolic factors, was used. A descriptive analysis was employed to report the associations between disability measures and the presence/absence of specific risk factors, accounting for diagnoses and the age of patients.

Results A total of 64 studies (97,846 patients) were included, and a total of 86 single associations were found. Metabolic risk factors (high BMI, high fasting plasma glucose, and LDL cholesterol), and behavioural risk factors (low

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physical activity, inadequate dietary habits, tobacco smoking, and alcohol consumption) were the most frequently reported.

Conclusions Our results suggest that it is possible to address headache-related disability by acting on a set of modifiable factors, with interventions tailored to the specific needs of patients or addressing the exposed populations as a whole. In particular, targeting dietary aspects and exercise is reasonably expected to promote weight loss, and might have an impact on the reduction in fasting plasma glucose and LDL cholesterol, ultimately improving patients' overall health status and reducing headache-related disability.

Keywords Migraine, Headache, BMI, Fasting plasma glucose, LDL cholesterol, Physical activity, Dietary habits

Introduction

Primary headache disorders are among the most prevalent conditions worldwide, affecting 2.9 billion people, and represent a leading cause of disability, as measured by Years Lived with Disability (YLDs) in the Global Burden of Disease Study (GBD) [1, 2]. Tension-type headache (TTH) is the most prevalent primary headache, typically associated to a low individual disability [3], while migraine, though less prevalent, is responsible for a substantially higher health loss [4]. This burden is expected to further increase among young adults aged 30–44 years, by 20% for migraine and 26% for TTH over the next 20 years, as a result of the population growth in size and of demographic shifts [5]. Cluster headache (CH), despite extremely disabling at the individual level [6], is not included among GBD estimates due to its low prevalence. The disability caused by primary headaches is determined by a complex interplay between clinical features, beyond attacks frequency and severity, and personal factors, including age, sex, employment status, socio-economic conditions, psychological comorbidities, and access to care [3, 4, 6]. Understanding these factors is crucial for assessing headaches' burden and identifying opportunities for intervention.

Recent therapeutic advances, particularly the development of calcitonin gene-related peptide (CGRP)-targeted treatments, have changed the management of migraine [7]. However, these therapies are ineffective for TTH [8], and their efficacy in CH remains inconsistent [9–11]. These new therapies have been shown to be cost saving [12], but differences in dispensation based on socio-economic status exist [13], raising concerns about healthcare equity as highlighted by UN Sustainable Development Goal 3 (SDG-3) and by the WHO Intersectoral Global Action Plan on Epilepsy and Other Neurological Disorders (WHOiGAP), which call for universal access to neurological care as a way to reduce the burden of neurological diseases [14, 15]. These two documents, in the perspective of headache disorders, point out several actions to reduce the burden of headache disorders, *e.g.* providing effective services for diagnosis, treatment and care, and implementing strategies for health promotion and headache prevention [16, 17]. Among the actions that have been addressed as relevant, recognizing and managing comorbid diseases and risk factors were included.

The issue of risk factors in headache disorders is of relevance, but not systematically explored. In fact, several factors, usually identified as headache triggers, influence headache occurrence, particularly migraine. These include foods (*e.g.* alcohol, chocolate, caffeine-containing products, processed foods, seafood, fish, ice cream, foods containing nitrates or tyramine), behavioural factors (*e.g.* reduced sleep, smoking, stress or physical inactivity), physical factors (*e.g.* the myofascial trigger points), and finally environmental ones (*e.g.* noise, smell or light) [3, 4, 6]. These factors are, however, studied in relation to single headache attacks and are included in patietns' education programs [18, 19], but are not generally included in systematic analyses on their impact on disability or disease burden: thus, the share of disability that might be avoided by acting on specific factors is unknown.

GBD regularly produces estimates of global health loss stratified by age, location, and sex [1]. The study quantifies disease burden using Disability-Adjusted Life Years (DALYs) which is a measure encompassing health loss due to premature mortality (Years of Life Lost – YLLs) and to non-fatal outcomes (YLDs). GBD also systematically produces estimates of the amount of burden that is attributable to a set of 88 risk factors, roughly categorized as environmental and occupational, behavioural, and metabolic [20]. These risk factors are conceptualized as share of deaths, YLLs, YLDs, or DALYs that can be attributed to – i.e., estimated to occur due to – exposure to a particular risk factor, and their control is therefore expected to contribute to a reduction of mortality, YLLs, YLDs, or DALYs associated to a condition. The quantification of risk factors is however still uneven: with reference to neurological disorders, risk factors quantification is available only for stroke (18 factors), encephalitis and meningitis (4 factors), dementias (3 factors), and for multiple sclerosis, Parkinson's disease, idiopathic epilepsy, and idiopathic intellectual disability (1 factor each) [2]. No quantification is available for headache disorders.

Pharmacological interventions are unlikely to be sufficient to reduce the burden of headache disorders as they are not expected to produce a global impact on population-level disability [16, 17]. Healthcare strategies need to address modifiable risk factors relevant for headache disorders, otherwise the likelihood of reducing their burden will be minimal, as witnessed by the substantial stability of YLDs associated to migraine and TTH [21, 22].

Therefore, identifying the risk factors which are relevant to headache disorders is essential to determine how much of the headache-related disability could be prevented or reduced through targeted interventions addressing specific risk factors. This systematic review summarizes which risk factors, as classified in the taxonomy of the GBD, are associated to disability in primary headaches: this information is intended to stimulate the GBD to incorporate risk factors analysis also for headache disorders which, in turn, could provide useful inputs to plan interventions aimed at reducing headache-related disability worldwide.

Methods

A literature review with meta-analysis was performed and results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [23].

Search strategy

Two main terms with possible variations and outcomes, *i.e.* primary headache disorders and disability, were searched in PubMed, Web of Science and SCOPUS, using database-specific variations, in the period between 2000 and 2025. In particular, in addition to the generic terms disability and impact, the acronyms of the most used Patient-Reported Outcome Measures (PROMs) for disability, as per the results of previous reviews [24, 25], were included.

The PubMed string was: ((“Migraine”[Title/Abstract] OR “tension type headache”[Title/Abstract] OR “tension type headache”[Title/Abstract] OR “Cluster Headache”[Title/Abstract]) AND (“disability”[Title/Abstract] OR “impact”[Title/Abstract] OR “MIDAS”[Title/Abstract] OR “HIT-6”[Title/Abstract] OR “WHODAS”[Title/Abstract] OR “HDI”[Title/Abstract])) AND ((english[Filter]) AND (2000:2025[pdat])).

The SCOPUS string was: ((TITLE (migraine OR “Tension-Type Headache” OR “Tension Type Headache” OR “Cluster Headache”) AND TITLE (disability OR impact OR midas OR “HIT-6” OR whodas OR hdi))) OR ((ABS (migraine OR “Tension-Type Headache” OR “Tension Type Headache” OR “Cluster Headache”) AND ABS (disability OR impact OR midas OR “HIT-6” OR whodas OR hdi))) AND PUBYEAR > 1999 AND PUBYEAR < 2026 AND (LIMIT-TO (LANGUAGE, “English”)).

The Web of Science string was: (Migraine OR “Tension-Type Headache” OR “Tension Type Headache” OR “Cluster Headache” (Abstract) AND disability OR impact OR MIDAS OR “HIT-6” OR WHODAS OR HDI (Abstract)) OR (Migraine OR “Tension-Type Headache” OR “Tension Type Headache” OR “Cluster Headache” (Title) AND disability OR impact OR MIDAS OR “HIT-6” OR WHODAS OR HDI (Title)) AND (2024 OR 2021 OR 2023 OR 2022 OR 2020 OR 2019 OR 2018 OR 2017 OR 2016 OR 2015 OR 2013 OR 2012 OR 2014 OR 2025 OR 2011 OR 2010 OR 2009 OR 2008 OR 2006 OR 2007 OR 2005 OR 2004 OR 2003 OR 2002 OR 2001 OR 2000 (Publication Years)) and English (Languages).

Retrieved references were exported as .csv files and imported to Rayyan QRCI [26] for duplicate checking. The set of records was then exported to Micrisoft Excel for study selection and data extraction.

Study selection

Retrieved references were equally and randomly assigned to the authors to perform the title and abstract checks. In this phase, records were retained if they were primary research papers reporting information on disability associated to one of the three main primary headaches, *i.e.* migraine, TTH and CH. Therefore, records were excluded if they: a) did not have an abstract; b) were not in English; c) were published before 2000; d) were letters, editorials, conference material, book chapters, case reports with less than 10 subjects, or literature reviews; e) did not report on primary headache disorders; f) were clearly out of topic, i.e. did not address elements associated to or predictive of primary headache disability/impact. In this stage, we employed a conservative approach; therefore, in case of doubts, especially on the last criterion, the indication was to retain the record so that its full-text could be appropriately evaluated.

A double check procedure on titles and abstracts eligibility was randomly performed on 30% of selected references: AdP, AO, BR, DO, ER–B, LP, and MW–P performed the double check on abstracts. In this phase, the agreement among reviewers (i.e. the inter-rater reliability) was calculated using Krippendorff’s alpha coefficient (α), which ranges between 0 (total disagreement) and 1 (total agreement). In case of disagreement, the record was considered as selected and retained for full-text evaluation. If Krippendorff’s α was below 0.70, a second 30% set of references were submitted to double-check.

Eligible references were equally and randomly assigned to the authors who screened titles and abstracts, and, as a further control measure, a shuffle procedure was employed so that none of the authors had to evaluate a set of full texts that they previously handled at the abstract check. In the phase of full-text evaluation, studies were excluded if they: a) were not in English; b) were not on primary headaches; c) were letters, editorials, conference material, book chapters, case reports with less than 10 subjects, or literature reviews; d) did not employ any disability PROMs; e) did not report any kind of association with a pre-defined list of risk factors based on GBD taxonomy. At this stage, the authors also performed data extraction.

The same authors (AdP, AO, BR, DO, ER–B, LP, and MW–P) performed a double check on 30% of the full texts, and Krippendorff's α was again calculated. In this phase, disagreement was resolved by a third rater (AR). If Krippendorff's α was below 0.70, a second 30% set of references were submitted to double-check.

Data extraction

Data extraction was performed through an *ad hoc* electronic spreadsheet of Microsoft Excel.

The GBD taxonomy includes a total of 88 risk factors, which are hierarchically organized up to four levels [20]. The three broad areas (environmental and occupational, behavioural, and metabolic factors) constitute level 1, and levels 2–4 gain higher specificity. For example, among behavioural risk factors, a level 2 factor is "Child and maternal malnutrition", which is then further broken down into six different level 3 factors, including "Suboptimal breastfeeding", which, in turn, is broken down into two different level 4 factors, namely "Non-exclusive breastfeeding" and "Discontinued breastfeeding". For the purpose of this review, we agreed upon a list of 24 factors (mostly level 2), which enabled us to cover the whole set of GBD-defined risk factors (see Supplementary Table 1 for the full list of risk factors herein employed). Our list included 7 environmental and occupational risk factors, 11 behavioural risk factors, and 6 metabolic risk factors.

For the purpose of this review, we selected the presence of any significant association between the risk factor and the PROM. Different scenarios were therefore envisaged, as shown in the example below, built around Body Mass Index (BMI), defined as weight in kg divided by square of height in meters) and the 6-item Headache Impact Test (HIT-6) [27]. Both have continuous scores and can be divided into subgroups, *e.g.* for BMI normal weight, overweight and obesity, and for HIT-6 little or no impact, some impact, substantial impact, and severe impact. The scenarios include: a) linear association models between HIT-6 and BMI score, such as linear correlations (*e.g.* Pearson's correlations) or categorical associations (*e.g.* chi-squared test); b) prediction models, such as linear regressions in which BMI predicts HIT-6, or logistic regression in which BMI grades predict HIT-6 grades; c) groups difference models, in which patients with different BMI grades show different HIT-6 scores (*e.g.* t-test, ANOVA or non-parametric equivalents); d) repeated measures designs, where variation in BMI is associated to variation in HIT-6.

Given the descriptive nature of this review, we just highlighted the presence of these connections: if at least one connection was reported, we collected information on diagnoses, total sample size, percentage of female patients and age. Finally, we assessed whether the HIT-6 [27] and the Migraine Disability Assessment (MIDAS) [28] were used jointly.

Data analysis

A descriptive analysis was employed to report the associations between disability measures and the presence/absence of specific risk factors, accounting for diagnoses and the age of patients. Although in some of the included papers a causal relation between exposure to a risk factor and disability as described with a PROM could be established, we always referred to "associations" because this was, in a sense, the common denominator across different possible approaches to data analysis used across papers.

If appropriate, a specific meta-analysis based on a previously developed 0–1 coefficient built upon MIDAS and HIT-6 [25] was carried out.

Results

After duplicate exclusion, a total of 7624 records were subject to selection, and of them, 64 were included in the review (see Fig. 1 for PRISMA diagram) [29–92]. Double check agreement was 0.838 at abstract check and 0.947 at full-text evaluation.

The majority of included studies, 53 out of 64, addressed migraine only [29–81], two studies addressed CH only [82, 83], one was on TTH only [84], three were on non-specified headache disorders [85–87], four were on mixed populations of migraine and TTH patients [88–91], and one paper was on a mixed population of patients with migraine and non-specified headaches [92]. A total of 97,846 patients were enrolled in the studies herein selected: the vast majority, *i.e.* 88,481, corresponding to 90.4% of the patients, had migraine; 7777 had TTH (7.9%), and the remaining 1.7% had either CH or non-specified headaches. Females number was available for 62 studies, for a total of 74,516 females out of 97,691 patients, corresponding to 76.3%. Almost all studies were on adult populations, three [79, 90, 92] were on paediatric patients, and two were on mixed populations of adolescents and young adults [44, 73].

Taken at the broad level, a total of 86 matches were found in 64 papers. The most common risk factors were behavioural ones (with a total of 53 matches), but the single most common factor was high BMI, reported in 21 studies. Table 1 presents an overview of the risk factors associated to disability in the three primary headache disorders. Detailed information on the content of the selected papers is available in Supplementary Material.

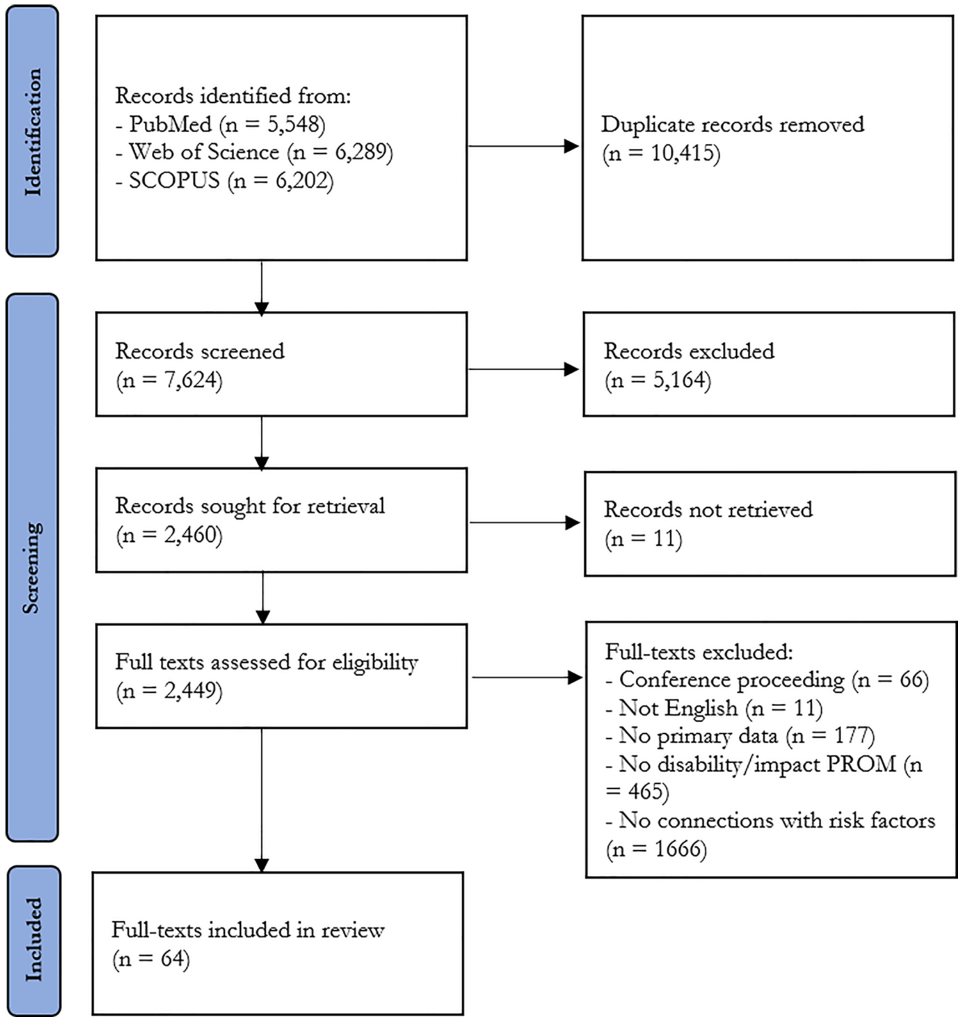

Fig. 1 Flowchart of study selection

Environmental and occupational risk factors

Environmental and Occupational Risk Factors were reported in four studies, for a total of four matches and 290 patients, 86.2% of whom had migraine [64, 67, 80, 91].

Few associations were found: the most common association was with climate issues, specifically non-optimal temperatures, retrieved in two studies on migraine patients. The association was, however, not clearly defined in terms of high or low temperature in one of the studies [67], whereas in the second it was associated to sunny periods in far northern regions [80].

Behavioural risk factors

Behavioural Risk Factors were reported in 39 studies, for a total of 53 single matches and 27,589 patients, 93.9% of whom with migraine [30, 33, 37–39, 41, 43–51, 53, 59–63, 65–68, 70, 73, 74, 76, 78, 79, 82–87, 89, 92].

The most commonly reported associations were with dietary habits, retrieved in a total of 14 different studies, of which 12 were conducted on patients with migraine [43, 46–51, 61, 68, 70, 74, 76], one on patients with TTH [84], and one on patients with non-specified headache disorders [87]. Results showed a negative effect of the scarce adherence to the Mediterranean diet, rather than of a poor-variety diet: in particular, high consumption of processed meat, sweetened beverages and high salt intake, as well as low consumption of fruit/vegetables, whole grains and omega-3 fatty acids were associated to a worse disability profile.

Nine studies reported a negative impact of low physical activity and disability, both in patients with migraine [47, 54, 59, 60, 63, 65, 78, 92] and in patients with non-specified headache disorders [86, 92]. Such a factor was sometimes simply referred to as "exercising regularly", whereas in other papers a precise indication of the amount of activity, which is considered as a gold standard or prescribed as part of a clinical trial (*e.g.* at least 150 min/week moderate exercise [93]), was reported.]). Also, the concept of effort related to physical activity is

Table 1 Overview of risk factors for disability in primary headaches

Risk Factors	No. of Studies with association	Migraine	TTH	CH	Not specified	All Patients	% of females
All Available Risk Factors	**64**	**88,481**	**7777**	**379**	**1209**	**97,846**	**76.3%**
Environmental & occupational risks	**4**	**250**	**40**			**290**	**74.5%**
Non-optimal temperature (High/Low)	2	120				120	90.8%
Occupational exposure to carcinogens, pollution, and other chemicals	1	90				90	NR
Occupational exposure to noise	1	40	40			80	50.0%
Behavioural risks	**39**	**25,928**	**86**	**379**	**1196**	**27,589**	**78.7%**
Tobacco smoking	8	18,549		172		18,721	77.3%
High alcohol use	7	1432	62	207	92	1793	80.0%
Drug use (illicit)	2	11,674				11,674	75.5%
Diet low in fruit, vegetables, legumens, whole grains, nuts & seeds, milk, fiber, calcium, omega-3 fatty acids omega-6 fatty acids	10	1639			84	1723	84.2%
Diet high in red meat, processed meat, sugar-sweetened beverages, trans fatty acids, sodium/salt	11	2294	24		84	2402	84.4%
Intimate partner violence	2	866			92	958	78.0%
Childhood sexual abuse and bullying	4	3258				3258	87.4%
Low physical activity	9	1264			1029	2284	73.2%
Metabolic risks	**26**	**80,481**	**7651**		**13**	**88,145**	**75.8%**
High fasting plasma glucose	4	12,258				12,258	76.5%
High LDL cholesterol	3	12,078				12,078	76.2%
High systolic blood pressure	1	11,837				11,837	76.0%
High BMI	21	79,819	7651		13	87,483	75.3%

Note. LDL, Low-Density Lipoprotein; BMI, Body Mass Index; TTH, Tension-Type Headache; CH, Cluster Headache

variable: referred to a self-description, measured through heart rate (e.g. 65% of age-specific maximum heart rate), or measured with perceived exertion scales [94].

Eight studies highlighted a negative impact of tobacco smoking on the disability of patients. Seven of them were on patients with migraine [30, 33, 44, 45, 47, 66, 73] and one on patients with CH [82]. All studies on migraine divided patients as active smokers and non-smokers, whereas the study on CH addressed the number of smoked cigarettes, smoking duration and implemented a smoking index, *i.e.* the product of the number of cigarettes smoked per day by the total number of years in which patients had smoked, which enabled addressing both group comparisons and linear relationships with smoking severity.

The association with alcohol use was explored in seven studies, and this was the only risk factor which was studied across all primary headaches: four studies were on patients with migraine only [41, 43, 67, 73], one on patients with CH only [83], one on patients with non-specified headache [85], and one mixing patients with migraine or TTH [89]. In all these studies, alcohol consumption was recorded as presence *vs.* absence of intake, with no consideration of the amount of intake, defined with standard drinks and therefore with categories based on frequency and quantity of intake (*e.g.* occasional drinkers vs. heavy drinkers [95]).

Themes connected to violence and abuse were reported in a total of five different manuscripts [37–39, 62, 85]: childhood abuse and bullying in relation to adult migraine-related disability were reported in four manuscripts [37–39, 62]; two studies addressed adult partner violence in relation to disability in both migraine and non-specified headache patients [39, 85]. The theme of abuse was addressed both with single questions (*e.g.* have you ever experienced some kind of abuse such as emotional, verbal, physical or sexual?), or with questionnaires such as the Childhood Trauma Questionnaire (CTQ) which enables gathering information on childhood traumatic events addressing both abuse (physical, sexual, and emotional), and neglect (both physical and emotional) [96]. Emotional abuse, physical neglect, as well as witnessing abuse in the family were the traumatic experiences associated to headache disability. Intimate violence was also shown to be associated to post-traumatic stress disorder, based on a study on a sample of females with migraine [85].

Metabolic risk factors

Metabolic Risk Factors were reported in 26 studies, for a total of 29 single matches and 88,145 patients, 91.3% of whom with migraine [29–36, 40, 42, 44, 47, 52, 53, 55–58, 69, 71, 72, 75, 77, 81, 88, 90].

The most commonly addressed risk factor for higher disability was high BMI, which was the single most frequently addressed risk factor, both in terms of amount of studies (21 out of 64 included, *i.e.* 32.8% of the total) and in terms of the amount of patients in which such relation was observed (87,483 out of 97,877, corresponding to 89.4% of the total) [29–36, 40, 42, 44, 47, 52, 55, 56, 71, 72, 75, 77, 88, 90]. All studies addressing BMI as a risk factor included people with migraine, and two of them also had mixed populations of people with migraine and TTH [88], or with migraine, TTH, and non-specified headache [90].

With regard to other metabolic factors, high fasting plasma glucose was found in relation to disability in migraine patients in four different studies [29, 53, 58, 81], with different indicators of glucose metabolism being found to be associated to higher disability. High LDL (Low-Density Lipoprotein) cholesterol was found to be associated to disability in migraine patients in three studies [29, 57, 69], and high systolic blood pressure in one study [29]. Specifically, this study [29] was the only one in which all four retrieved metabolic risk factors were included in the analyses.

Risk factors by disease and age group

As previously mentioned, almost all studies were on adults with migraine. Two studies were on patients with CH, and they showed a relation with behavioural risk factors, namely alcohol use and tobacco smoking [82, 83]. Five were on patients with TTH, finding associations with the following: environmental & occupational factors, specifically occupational noise [91]; behavioural factors, specifically diet high in red meat, processed meat, sugar-sweetened beverages, trans fatty acids, sodium/salt, and alcohol use [84, 89]; the metabolic factors, specifically high BMI [88, 90].

With regard to the age of patients, five studies in total included adolescents [44, 73, 79, 90, 92], and of them, two had a mixed populations of adolescents and young adults [44, 73]. Two risk factors were reported twice, namely the metabolic factor high BMI, and the behavioural factor smoking, both in the studies on mixed populations [44, 73]. High alcohol use, illicit drug use and low physical activity were reported once in three different studies.

Employed disability measures

The disability measures that were most commonly used were the HIT-6 and the MIDAS [27, 28], which were used together in only four studies [43, 75, 76, 79], none of which on the same risk factor – high alcohol use, and diet high in red meat, processed meat, sugar-sweetened beverages, trans fatty acids, sodium/salt [43]; high BMI [75]; diet low in fruit, vegetables, legumes, whole grains, nuts & seeds, milk, fiber, calcium, omega-3, omega-6 fatty acids [76]; illicit drugs use [79] – which did not enable us to apply for further analyses. Few other measures were employed, including the MIGSEV and PARADISE-24 [97, 98].

Discussion

Taken as a whole, the results of the present review suggest that part of the disability related to headache disorders, and to migraine in particular, might be avoided by acting on a set of risk factors. In particular, metabolic risk factors (high BMI, high fasting plasma glucose, and LDL cholesterol) and behavioural risk factors (low physical activity, inadequate dietary habits, tobacco smoking, and alcohol consumption) are the most suitable for large-scale public health interventions. In fact, the risk factors herein reported have been most often studied in relation to headache attack occurrence, but not deeply in terms of their impact on the disability of patients or disease burden, which is the main reason for the limited number of eligible publications in relation to the amount of retrieved records, and the unsuitability for conducting meta-analysis using the previously developed 0–1 coefficient built upon MIDAS and HIT-6 [25]. In turn, such impossibility prevented us us from providing information on the causal direction and strength of the associations herein presented. Nevertheless, elements of interest have been found, and some hypotheses on the way in which the retrieved risk factors might play a role in the public health approach to headache disorders can be formulated.

High BMI and other metabolic factors

An increasing body of evidence indicates that excess body weight is an important modifiable risk factor for both the onset and progression of headache disorders, particularly migraine [99]. Epidemiological studies have consistently demonstrated a bidirectional association between elevated BMI and migraine: individuals with obesity show a higher prevalence of both episodic and chronic migraine, while recurrent migraine attacks can contribute to sedentary behaviour and weight gain. For example, a population-based meta-analysis found that overweight and obesity are risk factors for frequent or chronic migraine, particularly among women [100]. Another study observed that total body obesity (measured by BMI) and abdominal obesity are associated to higher migraine prevalence and increased attack frequency [101]. Increased BMI is a marker of disability, primarily due to mobility limitations and heightened pain sensitivity [102]. However, increased disability was also found in relation to migraine-specific outcomes. Therefore, it is reasonable to hypothesize that it is due to mechanisms that are shared between migraine and obesity, such as limitations in social situations and stigma

[103]. Consequently, factors related to the lived experience of having migraine and high BMI complement the biological underpinnings of migraine expression and pathophysiology.

The mechanisms underlying this relationship are multifactorial. Adipose tissue acts as an active endocrine organ, producing pro-inflammatory cytokines such as TNF-α and interleukins, which may exacerbate neuroinflammation and alter pain pathways [104]. Moreover, obesity is associated to insulin resistance, impaired endothelial function, and increased oxidative stress, all of which may modulate migraine susceptibility and chronicity and may contribute to increased cardiovascular risk [105]. In fact, according to the findings of the present study, among the metabolic risk factors addressed for higher disability, the most investigated was high BMI. Interestingly, despite the close interplay between BMI and lipid metabolism, particularly with LDL cholesterol levels, the relation with the latter was poorly examined. In one study, higher LDL cholesterol levels were significantly associated to increased migraine severity, supporting the hypothesis that dyslipidemia may contribute to headache burden through vascular and inflammatory mechanisms [106].

Given the high prevalence of both obesity and migraine in the general population, strategies targeting BMI represent a key component of large-scale preventive approaches. Integrating weight management into migraine care may not only improve headache outcomes but also reduce the burden of associated comorbidities such as cardiovascular disease and type 2 diabetes [105]. In particular, the results of the Chronic Migraine Epidemiology and Outcomes Study (CaMEO) [29] highlighted that patients with high cholesterol have a higher prevalence of chronic migraine, higher disability (as assessed with MIDAS score) and experience more allodynia and medication overuse. Another cross-sectional study that included 266 female patients observed a statistically significant correlation between higher consumption of calories, carbohydrates, proteins, and fats, with severe migraine pain and disability [53]. Hence, it is possible to hypothesize that these factors are involved in increased disability due to a reduction in pain thresholds. This is in agreement with the results of a recent single-blind, crossover, randomized, controlled trial, according to which ingesting 75 g glucose increases pain sensitivity, while decreasing pain inhibitory responses on pressure pain thresholds [107]. Clinical intervention studies also lend support to the idea that weight loss can improve migraine outcomes. In a randomized controlled trial, a very low-calorie ketogenic diet reduced monthly migraine days and severity compared to a hypocaloric balanced diet in overweight patients with high-frequency episodic migraine [76]. Bariatric surgery has likewise been associated to marked alleviation of migraine severity, shorter duration of attacks, and more migraine-free days in obese patients with migraine, compared to non-surgical weight loss methods [108]. Future, adequately designed and powered clinical trials are mandatory to confirm this hypothesis, along with preclinical studies aimed at elucidating the underlying mechanisms.

Low physical activity

Migraine patients often lead sedentary lives [109]; in fact, physical inactivity is one of the targets of the education programs of patients [18, 19]. However, physical inactivity might also be due to fears that exercise may trigger an attack—a concern based on prior exercise-induced episodes. To overcome this fear-avoidance cycle known as kinesiophobia, it is crucial that patients receive proper explanations about why, how, and when it is safe to exercise. In recent years, WHO guidelines on physical activity have been provided, suggesting that adults should undertake regular physical activity to improve several health domains (including overweight and obesity, hypercholesterolemia, and diabetes) as well as decrease mortality [110]. Exercise at appropriate intensity and timing—avoiding vigorous activity during the pre-ictal or ictal phases—has demonstrated effective outcomes by optimizing therapeutic windows.

Systematic reviews establish that aerobic exercise reduces migraine days [111, 112], while a randomized controlled trial showed that 40-minute sessions three times weekly over three months yielded improvements equivalent to topiramate prophylaxis [113]. In migraine patients with co-existing TTH, aerobic exercise has proven not only safe but also efficacious in reducing overall headache burden [114]. Strength training appears superior to aerobic exercise in reducing migraine burden [115], with a combination of muscle-strengthening and vigorous activities yielding a 52% reduction of migraine occurrence [116]. Integrating regular exercise with regular lifestyle behaviours – consistent sleep, hydration, mealtimes – is essential [117]. Pacing through gradual exposure enhances self-efficacy and mitigates psychological barriers [118], which might be beneficial also in terms of stigma reduction: by participating in group activities aimed to increase regular physical activity, patients have the opportunity to form social relationships, which, in turn, reduces isolation. Educating headache patients, particularly those with migraine, about the safety and benefits of exercise, explaining its mechanisms and the value of regular practice, improves adherence and cultivates a resilient and healthier lifestyle, as exercising regularly is also a way to reduce excess weight.

Dietary factors

The role of dietary factors in the burden of headache disorders is still debated, as it is difficult to precisely evaluate dietary habits. Diet changes widely among different individuals, and within the same individual over time. Moreover, it is difficult to keep track of nutrients, as the best method to monitor dietary habits is to administer food frequency questionnaires that, in most cases, are retrospective or cross-sectional, and do not depict the changing dietary habits of individuals over time. However, keeping track of dietary habits is of importance, as these are commonly recognised (or perceived) as triggers for headaches, particularly migraine headaches [119, 120].

Some foods, such as red wine, cheese, crustaceans, and chocolate, are often reported as triggers for migraine attacks [121]; however, the degree to which these might actually "provoke" a headache attack is debatable. For example, some of the most commonly recognised dietary factors (*e.g.* nitrite, tyramine, caffeine, fats and several condiments) were not differently reported by patients with episodic and chronic migraine [120]. Besides, diets rich in carbohydrates can contribute to worsening insulin resistance, which is impaired in individuals with migraine according to observational data [58, 122–125], and has been described as a risk factor for increased disability [58, 81, 124]. An unbalanced diet can also contribute to the development of overweight or obesity, which are associated to migraine chronification, as previously discussed [126], and to higher disability *per se*. For headache disorders different from migraine, the relationship between dietary factors and the burden of headache has not been adequately studied yet. A study in an the Asian population showed that chocolate and coffee were significantly associated to migraine compared to TTH [127]. Questionnaires and inventories that specifically address headache triggers should be developed to determine whether certain factors are disease-specific contributors to worsening health and disability across different headache disorders [120].

Some special diets can be used as a headache treatment. Low-calorie ketogenic diet is able to prevent migraine [128] and cluster headache attacks [129]. However, the ketogenic diet is a special and imbalanced nutritional regime that is different from usual diets, and should be limited to individuals not responding to preventive migraine drugs. There is no clear evidence to prescribe an "ideal diet" that fits for all and that should be recommended to prevent headache disorders. However, according to our findings, the Mediterranean diet seems to be the best regimen in individuals with headache who do not require dietary limitations or a special therapeutic nutritional regimen. To better address the role of dietary factors on headache burden, further large, prospective studies are needed both in migraine and in other headache disorders, with replicable methodology and clear results.

Tobacco and alcohol

Tobacco and alcohol consumption are among the most important behavioural and modifiable risk factors for all-cause YLDs: smoking was ranked as the third most important factor, and second among behavioural ones, accounting for 2.6% of all-cause YLDs; whereas high alcohol consumption was ranked as the eighth factor, and fourth among behavioural ones, accounting for 1.6% of all-cause YLDs [1]. Tobacco use is a well-known risk factor for the development of many chronic diseases [105, 130]. The exact relationship between nicotine use or exposure and primary headaches remains unknown. In a recent meta-analysis of 37 studies, the overall prevalence of tobacco smoking in primary headaches was 32% [131]. The prevalence was 20% among migraine patients, 19% among those with TTH and 65% among those with cluster headache. Current smoking is also associated to an increased risk of migraine and a reduced risk of TTH. This review found no association between past smoking and migraine, and no association between current smoking and cluster headache [131], despite such an association being previously observed [82, 132], and a recent genome-wide association study meta-analysis indicated that smoking is a causal risk factor for cluster headache [133].

Many migraine patients believe that smoking worsens their condition, although this relationship has not been clearly established over the past 50 years. In one of the earliest studies, Volans and Castleden reported that half of the patients believed that smoking increased the intensity of their migraine pain [134], with similar results reported more recently by López-Mesonero and colleagues [135]. Another study involving 4,560 participants from the National Health and Nutrition Examination Survey found that, among adults who had never smoked, heavy exposure to environmental tobacco smoke, reflected by serum cotinine concentrations (a marker of tobacco exposure), was significantly associated to severe headache or migraine [136]. Despite their widespread use among young people prone to primary headaches, the impact of electronic cigarettes has not been examined yet. The reason why smoking was found to be a risk factor for increased disability is unclear. A potential hypothesis is that smoking is associated, in migraine patients, to the development of cranial autonomic symptoms which are typical of trigeminal autonomic cephalalgias [137], and to higher severity, frequency, and duration of attacks [138–140].

Alcohol consumption has been associated to the occurrence of several types of headaches, including primary headache disorders such as migraine and cluster headache, and secondary ones, such as alcohol-induced headache, which can occur shortly after drinking, or several hours later (the so-called "*hangover headache*") [141]. Alcohol is also a major risk factor for chronic diseases regardless of age and gender. Among primary headaches, alcohol, particularly red wine, has long been considered a potential trigger for migraine attacks [142]. Red wine is the alcoholic beverage most frequently reported by patients to precipitate headache, while other alcoholic drinks, such as beer, white wine or spirits, appear to play a less consistent and generally weaker role. The higher triggering potential of red wine may be related to its richer content in biologically active compounds such as histamine and tyramine, which can influence vascular tone and modulate inflammatory pathways [143]. Nonetheless, the specific contribution of these components remains debated, as inter-individual variability in alcohol metabolism and sensitivity likely modulates the response. Retrospective studies indicate that about one-third of migraine patients report alcohol as a precipitating factor, although only around 10% identify it as a frequent or consistent trigger [144]. In contrast, prospective studies have shown a limited or absent role, suggesting that the apparent inverse association between alcohol consumption and migraine may reflect reverse causality, whereby individuals with migraine tend to avoid alcohol, rather than alcohol providing a protective effect [145]. A meta-analysis of 126,173 participants with migraine found that the risk of migraine in alcohol drinkers is approximately 1.5 times lower than in non-drinkers (RR 0.71, 95% CI 0.57–0.89). An explanation for this phenomenon may indicate that it is migraine that leads to alcohol avoidance, rather than alcohol playing a protective role against migraine [146].

The way in which alcohol consumption impacts disability is likely due to the increase in headache frequency and intensity, as well as the impact on the associated symptoms like osmophobia. However, it has to be acknowledged that the consumption of alcoholic beverages is an activity which is carried out in social situations, and the consumption of moderate alcohol consumption has been associated to better quality of life among healthy adults as well [147, 148], and quality of life is a domain which is well connected to disability among individuals with migraine [149, 150].

Other factors

Two risk factors were not commonly associated to disability outcomes, despite their relevance for the onset and maintenance of headache disorders (and migraine in particular), namely high blood pressure and experiencing interpersonal violence in childhood or adulthood.

Clinical studies suggest that hypertension contributes to the progression from episodic to chronic migraine, with shared mechanisms with migraine such as autonomic dysregulation, disturbed renin-angiotensin system, and endothelial dysfunction [151]. However, surprisingly, high blood pressure was identified as a factor associated to disability in migraine patients in only one study [29], despite its recognized significance as a common comorbidity in migraine [152–155] and the use of antihypertensive agents, including beta-blockers, angiotensin II receptor antagonists, and angiotensin-converting enzyme inhibitors as prophylactic treatments. This gap in the literature underscores the necessity for more focused research to further investigate the role of elevated blood pressure in migraine-related disability, which, to date, is unclear and likely due to an effect on the measurement of disability (*i.e.* reliance on the MIDAS). Demonstrating the association between hypertension and disability outcomes may provide valuable insights for targeted interventions, highlighting the importance of managing hypertension to potentially reduce migraine-related disability and improve overall patient prognosis.

Behavioural risk factors in children and adolescents represent a particularly relevant but still underexplored dimension in relation to primary headache disorders. Among behavioural and psychosocial risk factors, the role of violence and abuse deserves specific consideration. Evidence suggests that emotional, physical, and sexual abuse, as well as neglect, may have long-lasting consequences on headache-related disability [37, 156, 157]. Studies adopting both single-question assessments and validated tools such as the CTQ consistently indicate that exposure to abuse and neglect is associated to a higher risk of developing disabling headache conditions later in life. Emotional abuse, physical neglect, and witnessing domestic violence have emerged as particularly relevant predictors, with up to 40% of migraine patients reporting at least one adverse childhood experience. In pediatric populations, the link between bullying, peer victimization, and headache is of growing concern. Adolescents exposed to recurrent bullying show increased prevalence of both migraine and tension-type headache, with odds ratios ranging from 1.5 to 2.3 compared to non-victimized peers [158, 159]. These findings suggest a potential cumulative effect of psychosocial stressors during neurodevelopmental stages, which may amplify pain perception and contribute to symptom chronification. Intimate partner violence has also been associated to increased disability and comorbid post-traumatic stress disorder in adult women with migraine [160]. This suggests that early exposure to violence may interact with later adverse experiences to worsen the clinical course of headache disorders. Taken together, these observations highlight the need to systematically assess experiences of abuse and violence in both research and clinical practice. Early identification of at-risk children and adolescents, combined with psychosocial support and school-based interventions, can mitigate the long-term impact of these traumatic experiences [160]. Furthermore, integrating trauma-informed approaches into headache management could represent an important step toward more effective care.

Employed outcome measures

An aspect that has to be taken into consideration in the interpretation of these results is that most of the research results presented herein have been produced using the MIDAS questionnaire. This poses a practical issue with the interpretation of data as MIDAS items are based upon the frequency of headaches; in fact, they refer to the number of days in which activities were not carried out, or partially carried out due to headache [28]. The MIDAS might pose a relevant recall bias in patients who do not keep a headache diary, and therefore need to give responses "by eye". The reliability of MIDAS, in particular for patients with chronic headaches, was in fact previously raised [161], and it is possible to presume that, in the context of severe headaches, those days with lower pain intensity might not be recalled [162]. This is part of the rationale for developing composite disability indexes that enable integration of disability information which are based on the frequency of headache-related problems (i.e. the MIDAS), and information which also account for their severity, like those reported in the HIT-6 or in the WHODAS-2, which provide information that, although correlated, are neither overlapping nor transposable [149]. Unfortunately, MIDAS and HIT-6 were jointly used only in four studies, which prevented us from exploiting the available 0–1 coefficients [25] and from running a full meta-analysis.

Limitations

Limitations to this study include the following. First, we were unable to locate eleven studies despite attempts using institutional library resources and direct messages to the corresponding authors. Second, our analysis is limited to the observation of a relation between the exposure to a risk factor and the score to a disability measure. This situation might correspond to a variety of statistical relations, *e.g.* correlations or group differences. Therefore, the meaning of the observed relation might be variable, but the "direction" in the relation between disability measure and exposure to risk factor was maintained: the presence of risk factor was associated to worse disability profiles. Moreover, papers included in this review employed different PROMs to address disability, which conceptualized headache-related disability in different ways. For example, the MIDAS is based on the frequency of days in which patients experience limitations, whereas other measures conceptualized disability in terms of "severity of limitations". Our inability to apply for a meta-analysis exploiting the previously developed 0–1 coefficients [25], due to the substantial lack of studies employing the MIDAS and HIT-6 together, prevented us to from calculating an estimate of the associations between risk factors and the coefficient that was developed with the aim of informing future GBD iterations. Third, we relied on a specific and "*a priori*" definition of risk factor, which had a positive impact, *i.e.* the fact that it is a recognised and valid one. However, it also limited the scope of the present review by excluding factors which might worsen the clinical profiles of patients and probably their disability level, examples of this include inadequate hydration, irregular meals (*e.g.* skipping breakfasts), or irregular sleep-wake patterns. Fourth, caution should be given in the interpretation of our results as broadly referred to primary headache as a broad group, as most of the papers herein included were on migraine.

Conclusions

In conclusion, this review found that several risk factors as defined by GBD taxonomy are associated to disability outcomes in patients with primary headaches, and in particular with migraine, as most of the literature is on migraine. Our results suggest that it might be possible to address headache-related disability by acting on a set of modifiable factors, with interventions that might be either tailored to the specific needs of patients or address the exposed populations as a whole.

At present, the results of our systematic review do not provide an indication of the direction or strength of the association between the risk factors and headache-related disability, which is due to our inability to apply for a meta-analysis exploiting the previously developed 0–1 coefficients [25]. In fact, studies are lacking that enable a direct evaluation of the direction and strength of the association between exposure to risk factors and disability outcomes in patients with headache disorders. Should future studies demonstrate the presence of a strong association this would surely have profound public health implications, considering the high prevalence of headache disorders. A recently published meta-analysis of population studies found that the one-year headache prevalence among the most exposed group, *i.e.* adults aged 18–65 which likely comprises most of the world's workforce, is approximately 65%, with migraine prevalence (including both episodic and chronic migraine) being 25% of the population, thus higher than previously reorted [163].

Although our results do not enable to address how much of the headache-related disability might be attributed to the risk factors herein found, we believe that the evidence we gathered here is sufficient to argue that future analyses addressing such associations deserve being carried out, and that future iterations of the GBD should estimate what is the amount of YLDs that can be attributable to some of the risk factors herein identified. To get to this point, longitudinal studies investigating causality between these risk factors and headache-related disability are needed. In fact, actions targeting risk factors might reduce disability that patients experience in their daily lives, and maybe also prevent the development of headache attacks, or reduce the risk of their chronification. For example, a program targeting dietary aspects and exercise is reasonably expected to promote weight loss in those who need it, but also a reduction of fasting plasma glucose and LDL cholesterol: such interventions might therefore have an impact on disability reduction.

A recent editorial took a position on the opportunity to prioritise brain health strategies by incorporating neurological disorders within non-communicable disease (NCD) agendas. Including brain disorders, and therefore headaches, would give policy relevance to the strategies aimed to prevent disease onset and reduce their burden at population and individual levels, which is of relevance since brain disorders affect approximately 3.4 billion individuals globally [164]. However, it has to be noted that lack of inclusion of brain disorders among NCD agendas does not imply that public health interventions targeting NCDs such as diabetes, obesity, hypertension, and hypercholesterolemia cannot impact on brain disorders as well. Actually, brain disorders can largely benefit from policies against other NCDs [165]: what we are missing is the evidence on the amount of impact addressing risk factors common to many conditions may have for brain disorders, including headaches, which constitute the largest part of those with brain disorders (2.9 out of 3.4 billion individuals). This prevents us from directing health policies, and from evaluating their results: for this reason, research is needed to uncover how much health improvement and disability reduction can be achieved through these kind of intervention.

Abbreviations

BMI	Body Mass Index
CaMEO	Chronic Migraine Epidemiology and Outcomes Study
CGRP	Calcitonin Gene-Related Peptide
CH	Cluster Headache
CTQ	Childhood Trauma Questionnaire
DALYs	Disability-Adjusted Life Years
GBD	Global Burden of Disease Study
HIT-6	6-item Headache Impact Test
LDL	Low-Density Lipoprotein
MIDAS	Migraine Disability Assessment
NCDs	Non-communicable Diseases
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROMs	Patient-Reported Outcome Measures
SDG-3	Sustainable Development Goal 3
TTH	Tension-Type Headache
WHOiGAP	WHO Intersectoral Global Action Plan on Epilepsy and Other Neurological Disorders
YLDs	Years Lived with Disability
YLLs	Years of Life Lost

Supplementary information

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Supplementary Material 1

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Author contributions

Alberto Raggi planned the study, organized data search, the whole process of records screening and selection, drafted the introduction, methods, results and part of the discussion sections of the manuscript. Paolo Martelletti planned the study and supervised the whole manuscript. The remaining authors selected records, extracted data and drafted sections of the manuscript.

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