Al-Hassany *et al.*
The Journal of Headache and Pain (2025) 26:113
https://doi.org/10.1186/s10194-025-02060-w

The Journal of Headache and Pain

CORRESPONDENCE

Open Access

Unraveling the paradox: cardiovascular risk profiling in migraine– a correspondence

Linda Al-Hassany[1], Ruben W. A. van Drie[1,2], Deirdre M. Boucherie[1] and Antoinette MaassenVanDenBrink[1*]

Abstract

We read with great interest the recent publication by Marston and colleagues in Nature Medicine, entitled "Endothelial cell-related genetic variants identify LDL cholesterol-sensitive individuals who derive greater benefit from aggressive lipid lowering" (issue 31, March 2025, pages 963–969). Among their compelling findings, the association between the endothelial cell-specific polygenic risk score (EC-PRS) – which consists of SNPs associated with coronary artery disease – and a reduced risk of migraine headaches stood out, although not being the study's primary aim. Migraine imposes a substantial individual and socioeconomic burden worldwide. Beyond its neurological manifestations as a primary headache disorder, migraine has increasingly been recognized as an independent and underappreciated cardiovascular risk factor, linked to major cardiovascular and cerebrovascular events. However, the biological underpinnings of this association remain poorly understood, particularly since they do not appear to be mediated through traditional or atherosclerotic pathways, and they are not associated with established cardiovascular risk factors. In this Correspondence, we build upon the findings of Marston et al. and contextualize them within the broader framework of migraine as a neurovascular disorder. Drawing from translational evidence, we propose a conceptual model that integrates findings regarding EC-PRS into the complex biological interplay linking migraine and cardiovascular disease, including coronary artery disease. In doing so, we aim to advance our understanding of migraine not only as a neurological disorder but as a marker of vascular vulnerability with implications for future research regarding personalized cardiovascular prevention, including statin therapy.

Keywords Migraine, Cholesterol, Lipids, Cardiovascular Risk, Endothelial Dysfunction, Microvascular Dysfunction, Statins

Main Text

With great interest, we have read the paper entitled "*Endothelial cell-related genetic variants identify LDL cholesterol-sensitive individuals who derive greater benefit from aggressive lipid lowering*" by Marston and colleagues, recently published in Nature Medicine [1]. In this genome-wide association study, the authors investigated the modifying role of low-density lipoprotein cholesterol (LDL-C) levels on the association between single nucleotide polymorphisms that are linked to endothelial cell (EC) function and incident coronary artery disease. The study demonstrates that the EC-specific polygenic risk score (EC-PRS), comprising 35 single nucleotide polymorphisms, is an independent risk predictor of the development of coronary artery

This comment refers to the article available online at https://doi.org/10.1038/s41591-025-03533-w.

*Correspondence:
Antoinette MaassenVanDenBrink
a.vanharen-maassenvandenbrink@erasmusmc.nl
[1] Division of Vascular Medicine and Pharmacology, Department of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, PO Box 2040, Rotterdam 3000 CA, the Netherlands
[2] Division of Experimental Cardiology, Department of Cardiology, Erasmus MC, University Medical Center Rotterdam, Thoraxcenter, Rotterdam 3000 CA, the Netherlands

disease. This risk was modified by LDL-C levels, while the cardiovascular preventive benefit of LDL-C lowering therapies (i.e., statins and PCSK9 inhibitors) was the largest among individuals with higher EC-PRS.

Interestingly, the EC-PRS was associated with a decreased risk of migraine headaches (OR per 1 SD increase = 0.94 (95% CI 0.92–0.96)). Besides being classified as the number one disabling disorder in women under the age of fifty [2], migraine – especially with aura symptoms – is an underappreciated cardiovascular risk factor associated with major cardiovascular and cerebrovascular events, including ischaemic and hemorrhagic stroke as well as myocardial infarction [3]. Notably, the incidence rate of migraine with aura for cardiovascular events has been demonstrated to be higher than that of obesity, high triglycerides, and even LDL-C [4]. Paradoxically, in contrast to the majority of such traditional cardiovascular risk factors, migraine is not associated with large-vessel atherosclerosis [5]. Women with a history of migraine and symptoms of suspected cardiac ischaemia even showed lower angiographic coronary severity scores, and less severe angiographic coronary artery disease [6]. In addition, while most traditional cardiovascular risk factors, such as hyperlipidemia, diabetes mellitus, and obesity, are comorbid, especially with increasing age, such overlap has not been consistently observed with migraine [7]. Migraine could, therefore, rather be considered a "non-atherosclerotic" or "non-traditional" cardiovascular risk factor, whose association with cardiovascular disease might be mediated by alternative biological pathways.

One such proposed pathway is endothelial dysfunction, which involves oxidative stress and inflammation. Marston and colleagues mention two vasodilatory and vasoconstrictive mediators herein, namely nitric oxide and endothelin-1, that have opposite pathophysiological effects in coronary artery disease and migraine [1]. While endothelin-1 might indeed be involved in the acute phase of migraine attacks, in the aura phase in particular [8], data on the association between endothelial dysfunction and migraine in general are yet inconsistent and inconclusive [9]. Aside from methodological heterogeneity between studies, a more plausible explanation may be that endothelial dysfunction represents an early stage of atherosclerosis – a process that is not expected to be particularly more present among migraine patients based on previous clinical data on vascular calcifications and atherosclerosis. Whether this also explains the finding that EC-PRS was associated with a decreased risk of migraine headaches by Marston and colleagues [1] remains to be demonstrated.

An important consideration herein is the distinction between absolute plasma levels of mediators and their actual biological activity, which depends on their binding to specific receptors and subsequent activation leading to vasodilation or vasoconstriction. Thus, measurements of plasma concentrations do not inherently capture the effects of receptor (de)sensitization and, therefore, cannot be assumed to represent true biological activity in migraine patients. Taking this into account, we have applied a novel and non-invasive technique that induces local thermal hyperaemia of the skin of the forearm to study microvascular activity [10]. By applying blocking compounds, we differentiated between i) endothelium-dependent responses and ii) endothelium-independent responses. The first mechanism captures the contribution of nitric oxide bioavailability or endothelial dysfunction, while the latter captures the contribution of neuropeptide activity – a second proposed pathway that might be involved in the association between migraine and cardiovascular disease. Among middle-aged women, comparable in age to the cohort studied by Marston and colleagues [1] and with presumed elevated cardiovascular risk due to polycystic ovary syndrome, we observed no significant differences in endothelium-dependent vascular responses between those with and without migraine. However, neuropeptide action was observed to be lower compared with those without migraine [10]. While larger studies are warranted to replicate these findings, also in younger women and men, the absence of lower endothelium-dependent responses among migraine patients is consistent with data by Marston and colleagues [1].

Biology, however, unfolds with far greater complexity (Fig. 1). First, while calcitonin gene-related peptide (CGRP) is a key vasodilatory neuropeptide in migraine pathophysiology, serving as a target of novel anti-migraine therapies and a protective molecule under ischaemic circumstances, other neuropeptides – some exerting opposing effects – have also been implicated [11, 12]. Second, studies on lipid profiling and serum lipids are conflicting regarding the involvement of LDL-C in migraine [13, 14]. This is further complicated by the presence of aura – a factor not accounted for separately by Marston and colleagues [1] – and the migraine activity status. While we assume that Marston and colleagues [1] studied prevalent migraine in their analyses, we have shown that higher cardiovascular risk score categories were observed among women with a migraine history but not with active migraine at baseline or incident migraine [15]. Thus, migraine activity status influences cardiovascular risk status — and potentially lipid profiles — independent of age. Further research is warranted to understand the association between EC-PRS and the influence of different migraine

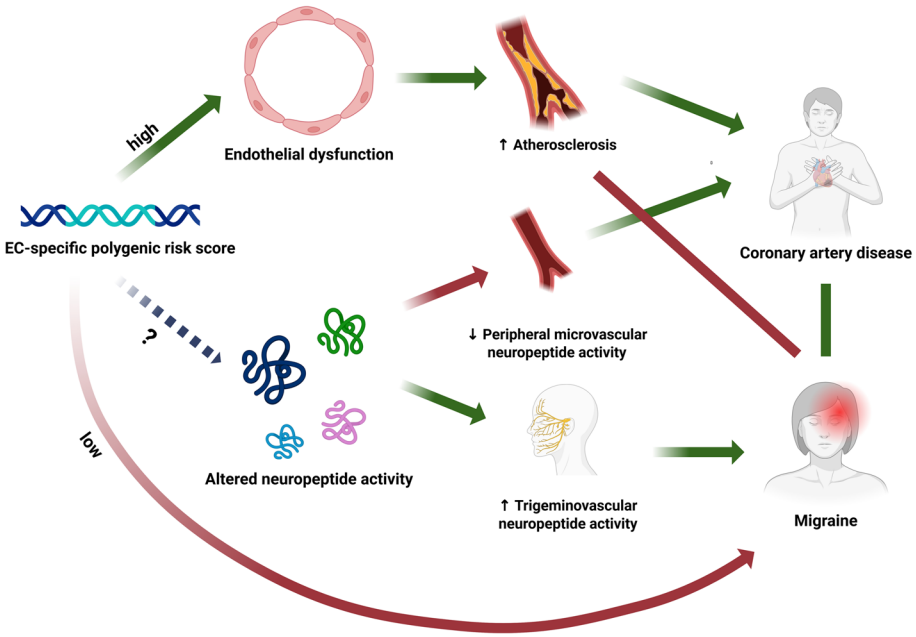

Fig. 1 – A hypothesized overview of biological mechanisms involved in the association between the EC-specific polygenic risk score, migraine, and coronary artery disease. Green arrows and lines represent stimulatory or upregulated effects, while red arrows and lines indicate inhibitory or downregulated effects. Please note that this is a simplified model and does not capture the full complexity of the interactions and (causal) effects involved. Image was created using *BioRender*

activity statuses while accounting for the potentially modifying influence of lipids. This is also relevant when considering statin therapy in migraine, given the possible association between the expression of the HMG-CoA reductase gene and an increased migraine risk, especially with aura – as evaluated in a recent systematic review and meta-analysis [16]. A recent Mendelian randomization study also demonstrated significant associations between lipid-modifying drug target genes and a lower risk of migraine, in particular with the enhancement of LPL (lipoprotein lipase) and inhibition of HMGCR (3-hydroxy-3-methylglutaryl-CoA reductase) [17]. While larger randomized studies are warranted, the potential efficacy of statins in reducing migraine frequency and triptan usage presents a promising novel (and relatively low-cost) adjunct preventive therapeutic option in the headache field. Importantly, since their effectiveness seems to vary based on lifestyle factors (such as smoking and alcohol use) and comorbid conditions, further research is warranted to better integrate these therapies into individualized treatment strategies [18]. Furthermore, the exact biological actions of these therapies in migraine patients – both, with and without hypercholesterolemia – represents an important area for further research. These actions include the role of neuropeptides involved in migraine pathophysiology and microvascular function, such as CGRP, but also pituitary adenylate cyclase-activating polypeptide (PACAP) and vasoactive intestinal peptide (VIP) [19].

In summary, the study by Marston and colleagues provides a clinically relevant tool to select individuals who would benefit most from lipid lowering therapy, and adds a meaningful piece to the intricate puzzle of migraine-related cardiovascular risk — even though this was not the study's primary aim. These findings will, hopefully, pave the way for research on improving cardiovascular risk assessment – and, eventually, personalized treatment, including statin use – in migraine patients.

Abbreviations

CGRP	Calcitonin gene-related peptide
CI	Confidence interval
EC	Endothelial cell
EC-PRS	EC-specific polygenic risk score
HMGCR	3-Hydroxy-3-methylglutaryl-CoA reductase
LDL-C	Low-density lipoprotein cholesterol
LPL	Lipoprotein lipase
OR	Odds ratio
PACAP	Pituitary adenylate cyclase-activating polypeptide
SD	Standard deviation
VIP	Vasoactive intestinal peptide

Acknowledgements

Figure 1 was created using *BioRender.com*.

Authors' contributions

Linda Al-Hassany: Paper concept; drafting and revision of the manuscript for content, including medical writing for content. Ruben W.A. van Drie: Paper

concept; revision of the manuscript for content, including medical writing for content. Deirdre M. Boucherie: Paper concept; revision of the manuscript for content, including medical writing for content. Antoinette MaassenVanDenBrink: Paper concept; revision of the manuscript for content, including medical writing for content; supervision. All authors read and approved the final manuscript.

Funding
This work was supported by the Dutch Research Council (ZonMw/NWO, Vici Grant (09150181910040).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
Linda Al-Hassany, Ruben W.A. van Drie, and Deirdre M. Boucherie declare that they had no conflict of interest with respect to the research, authorship, and/or publication of this article. Antoinette MaassenVanDenBrink received research grants and/or consultation fees from AbbVie, Amgen/Novartis, Eli Lilly, Lundbeck, Manistee, Pfizer, Satsuma, Teva, and Tonix.
Antoinette MaassenVanDenBrink received research grants and/or consultation fees from AbbVie, Amgen/Novartis, Eli Lilly, Lundbeck, Manistee, Pfizer, Satsuma, Teva, and Tonix.

Received: 24 April 2025 Accepted: 1 May 2025
Published online: 13 May 2025

References

1. Marston NA, Kamanu FK, Melloni GEM, Schnitzler G, Hakim A, Ma RX et al (2025) Endothelial cell-related genetic variants identify LDL cholesterol-sensitive individuals who derive greater benefit from aggressive lipid lowering. Nat Med 31(3):963–969
2. Steiner TJ, Stovner LJ, Jensen R, Uluduz D, Katsarava Z, Lifting The Burden: the Global Campaign against Headache. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. J Headache Pain. 2020 Dec 2;21(1):137.
3. Mahmoud AN, Mentias A, Elgendy AY, Qazi A, Barakat AF, Saad M et al (2018) Migraine and the risk of cardiovascular and cerebrovascular events: a meta-analysis of 16 cohort studies including 1 152 407 subjects. BMJ Open 8(3):e020498
4. Kurth T, Rist PM, Ridker PM, Kotler G, Bubes V, Buring JE (2020) Association of Migraine With Aura and Other Risk Factors With Incident Cardiovascular Disease in Women. JAMA 323(22):2281–2289
5. van Os HJA, Mulder IA, Broersen A, Algra A, van der Schaaf IC, Kappelle LJ et al (2017) Migraine and cerebrovascular atherosclerosis in patients with ischemic stroke. Stroke 48(7):1973–1975
6. Ahmed B, BaireyMerz CN, McClure C, Johnson BD, Reis SE, Bittner V et al (2006) Migraines, angiographic coronary artery disease and cardiovascular outcomes in women. Am J Med 119(8):670–675
7. Al-Hassany L, Acarsoy C, Ikram MK, Bos D, MaassenVanDenBrink A (2024) Sex-Specific Association of Cardiovascular Risk Factors With Migraine: The Population-Based Rotterdam Study. Neurology 103(4):e209700
8. Iljazi A, Ayata C, Ashina M, Hougaard A (2018) The role of endothelin in the pathophysiology of migraine-a systematic review. Curr Pain Headache Rep 22(4):27
9. Sacco S, Ripa P, Grassi D, Pistoia F, Ornello R, Carolei A et al (2013) Peripheral vascular dysfunction in migraine: a review. J Headache Pain 14(1):80
10. Al-Hassany L, Linstra KM, Meun C, van den Berg J, Boersma E, Danser AHJ et al (2023) Decreased role of neuropeptides in the microvascular function in migraine patients with polycystic ovary syndrome. Atherosclerosis 384:117172
11. Al-Hassany L, Goadsby PJ, Danser AHJ, MaassenVanDenBrink A (2022) Calcitonin gene-related peptide-targeting drugs for migraine: how pharmacology might inform treatment decisions. Lancet Neurol 21(3):284–294
12. Al-Hassany L, Boucherie DM, Creeney H, van Drie RWA, Farham F, Favaretto S et al (2023) Future targets for migraine treatment beyond CGRP. J Headache Pain 24(1):76
13. Onderwater GLJ, Ligthart L, Bot M, Demirkan A, Fu J, Van Der Kallen CJH et al (2019) Large-scale plasma metabolome analysis reveals alterations in HDL metabolism in migraine. Neurology 92(16):E1899–E1911
14. Liampas I, Mylonas KS, Brotis A, Dervenis P, Siokas V, Mentis AFA et al (2021) Serum lipid abnormalities in migraine: A meta-analysis of observational studies. Headache 61(1):44–59
15. Ibrahimi K, Rist PM, Carpenet C, Lee Rohmann J, Buring JE, Maassen van den Brink A, et al. Vascular Risk Score and Associations With Past, Current, or Future Migraine in Women: Cohort Study. Neurology. 2022 Aug 19;99(16):e1694–701.
16. Makhlouf HA, Hassan AK, Almosilhy NA, Osman ASA, Ramadan S, Abouelmagd ME (2025) Exploring the association between statins use or HMG-CoA reductase inhibition and migraine: a systematic review and meta-analysis. J Headache Pain 26(1):23
17. Bi Y, Zhu Y, Tang S, Huang Y (2023) Lipids, lipid-modifying drug target genes and migraine: a Mendelian randomization study. J Headache Pain 24(1):112
18. Kang HS, Kim JH, Kim JH, Bang WJ, Yoo DM, Lee NE, Han KM, Kim NY, Choi HG, Min KW, Kwon MJ (2024) The Association between Statin Use and Reduced Migraine Likelihood: A Comprehensive Analysis of Migraine Subtypes and Statin Types in a Nationwide Korean Cohort. Pharmaceuticals (Basel) 17(8):1056
19. Al-Hassany L, Boucherie DM, Creeney H, van Drie RWA, Farham F, Favaretto S, et al. on behalf of the European Headache Federation School of Advanced Studies (EHF-SAS). Future targets for migraine treatment beyond CGRP. J Headache Pain. 2023 Jun 28;24(1):76.

Publisher's Note