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ORIGINAL RESEARCH ARTICLE

Hyperemesis gravidarum: Associations with personal and family history of nausea

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Abstract

Introduction: The pathogenesis and risk factors for hyperemesis gravidarum, excessive nausea and vomiting of pregnancy, are not adequately recognized. In our previous study, we found that women with a personal history of nausea in different situations and a family history of nausea and vomiting of pregnancy (NVP) were more likely to have severe NVP. The present study focuses on these themes in association with hyperemesis gravidarum in a hospital setting.

Material and methods: Women with hyperemesis gravidarum ($n = 102$) were recruited from among patients hospitalized due to hyperemesis gravidarum in Turku University Hospital, Finland. Our control group (Non-NVP group, $n = 138$) consisted of pregnant women with no NVP. Personal history of nausea in different situations was inquired about in relation to "motion sickness", "seasickness", "migraine", "other kind of headache", "after anesthesia", "during the use of contraception", and "other kinds of nausea". Relatives with NVP were divided into first-degree (mother and sisters) and second-degree (more distant) relatives.

Results: In univariate analysis, a personal history of motion sickness, seasickness, nausea related to migraine, nausea with other headache and nausea in other situations were associated with hyperemesis gravidarum. After adjusting for age, parity, pre-pregnancy body mass index, marital status, and smoking, motion sickness (adjusted odds ratio [aOR] 5.24, 95% confidence interval [CI] 2.67–10.31, $p < 0.0001$), seasickness (aOR 4.82, 95% CI 2.32–10.03, $p < 0.0001$), nausea related to migraine (aOR 3.00, 95% CI 1.58–5.70, $p < 0.001$), and nausea in other situations (aOR 2.65, 95% CI 1.13–6.20, $p = 0.025$) remained significant. In multivariable analysis with all history of nausea variables, motion sickness (OR 2.76, 95% CI 1.29–5.89, $p = 0.009$) and nausea related to migraine (OR 3.10, 95% CI 1.40–6.86, $p = 0.005$) were associated with hyperemesis gravidarum. Having any affected relative (OR 3.51, 95%CI 1.84–6.73, $p = 0.0002$), especially a first-degree relative (OR 3.06, 95% CI 1.62–5.79,

Abbreviations: 5-HT, 5–hydroxytryptamine; aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; GDF15, growth/differentiation factor 15; HG, hyperemesis gravidarum; NVP, nausea and vomiting of pregnancy; OR, odds ratio; PUQE, pregnancy-unique quantification of emesis.

$p = 0.0006$), was also associated with hyperemesis gravidarum. Adjustment did not change the results.

Conclusions: Women with a personal history of nausea or a family history of NVP are more likely to suffer from hyperemesis gravidarum. These results are beneficial to better identify and help women at risk for hyperemesis gravidarum.

KEYWORDS

hyperemesis gravidarum, migraine, motion sickness, nausea, nausea and vomiting of pregnancy, relatives, woman

1 | INTRODUCTION

Nausea and vomiting are very common symptoms in early pregnancy. In up to 3.6% of pregnancies the symptoms are severe, and the condition is referred to as hyperemesis gravidarum (HG).[1] By definition, women suffering from HG have nausea and vomiting starting in early pregnancy, inability to eat and/or drink normally, and symptoms that strongly limit the daily living.[1] Often these symptoms lead to dehydration and weight loss. HG is the most common reason for hospitalization in early pregnancy,[2] and has a major impact on women's health and may even influence family planning in the future.[3] Nevertheless in clinical practice, recognition of HG by healthcare personnel is insufficient, and therefore patients are often underdiagnosed and undertreated.

The pathogenesis of HG is not adequately recognized, but previous research suggests that the etiology is likely to be multifactorial.[4] Both general nausea and vomiting and HG stem from a similar background, as vestibular, olfactory, hormonal and gastrointestinal pathways are known underlying factors for both conditions.[5–7] Nausea and vomiting are common in migraine, as well as in seasickness, motion sickness, and after anesthesia, and are reported also with the use of oral contraception.[8–11] Disturbances in the vestibular system can provoke nausea, and vestibular system abnormalities have been described in HG.[12] Nausea in different situations and HG share similar elements, so it is plausible that a woman with a history of nausea would be more likely to have HG. However, there is a lack of knowledge regarding this connection. Furthermore, research elucidating a family history of HG is sound, as there is growing, although scant, evidence of familial aggregation of HG.[13–16]

In our earlier study with various severities of nausea and vomiting of pregnancy (NVP),[17] we found that women with a history of nausea were more likely to have more severe NVP. Furthermore, women whose relatives were affected by NVP had higher susceptibility for NVP themselves. In the present study, we aimed to evaluate the associations of personal history of nausea and NVP in relatives in women diagnosed with HG in a hospital setting. We hypothesized that, similarly to women with NVP, women with HG would be more prone to have personal and family histories of nausea. These results could provide tools for healthcare personnel to better identify women at risk for HG. Furthermore, the findings can be used in modern family planning counseling and even in the development of specific treatment for HG.

Key message

Women with a personal history of nausea, especially motion sickness and nausea related to migraine were more likely to suffer from hyperemesis gravidarum. Also, family history of nausea and vomiting of pregnancy was associated with occurrence of hyperemesis gravidarum.

2 | MATERIAL AND METHODS

This study was part of a larger HG study evaluating associative factors for HG. Women hospitalized due to HG in the antenatal ward of Turku University Hospital, Turku, Finland, in 2011–2019 were invited to participate. HG was diagnosed using the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10; O21.0, O21.1, and O21.9).[18] The decision on hospitalization for HG was based on current guidelines of the hospital and on the professional discretion of a specialist in obstetrics and gynecology concerning general sickness of the women due to HG, as well as clinical signs or laboratory findings of dehydration or presence of urinary ketones. Also, other reasons for nausea and vomiting were excluded. The Pregnancy-Unique Quantification of Emesis questionnaire (PUQE, Appendix S1),[19] was also filled in by the women in the HG group; however, it was not used as a criterion for hospitalization. Altogether, 105 women with HG participated (HG group), of which four pregnancies were twin pregnancies. However, the questionnaire was incomplete in three women, leaving the data of 102 women in the HG group for analysis.

Our control group ($n = 138$) was drawn from a larger cohort aimed to assess the severity of NVP in women attending routine maternity healthcare clinic visits during mid-pregnancy. The women ($n = 2411$) were recruited from 33 maternity healthcare clinics around the Turku city area between 2011 and 2014 during their regular mid-pregnancy visits by their maternity healthcare clinic nurses. The occurrence of NVP was evaluated by PUQE at or before 20 weeks of gestation as designated by the inclusion criteria. Of all the women, 286 (12.0%) had no NVP (PUQE = 3); and of these, 138 (5.7%) had complete responses to history of nausea and family history of NVP variables and participated by the end of 20 weeks of gestation, so were included in this study.

Basic characteristics of the HG group were collected from the hospital's medical records and data of the Non-NVP group from the Medical Birth Register of the Finnish Institute for Health and Welfare. Data included gestational week, parity, pre-pregnancy body mass index (BMI, kg/m^2), smoking (yes/no), and marital status (cohabiting/single). In addition, age was assessed, which in the HG group was counted from date of birth and date of hospitalization, and in the Non-NVP group from date of birth and date of answering the questionnaire. The basic characteristics of the groups are shown in Table 1. The two groups had differences regarding parity and smoking: compared with the Non-NVP group, there were more multiparous women in the HG group. Smoking was rare in both groups, but in the Non-NVP group, there were more smokers.

Participants were asked to fill in a questionnaire concerning their personal history of nausea in different situations: "motion sickness", "seasickness", "migraine", "other kind of headache", "after anesthesia", "during the use of contraception", and "other kind of nausea" (yes/no). Open questions were used to specify possible affirmative answers regarding "other kind of nausea" and "use of contraception". NVP of the relatives was inquired (yes, no, I do not know; if yes who?), and the answers were categorized into "first-degree" (mother, sister) and "second-degree" (aunt, cousin, grandmother, more distant) relatives. The questionnaire was distributed and answered in paper format and manually entered in electronic format by the researchers (Appendix S1).

2.1 | Statistical analyses

Continuous variables were presented using means and standard deviations or medians and interquartile ranges, and ranges of the values and categorical variables were characterized with percentages and frequencies. Missing replies were excluded from the analysis. Chi-squared test or Fisher's exact test were used in group comparisons. Two-sample *t* test was used with continuous normally distributed variables and Mann–Whitney *U* test with continuous variables that were not normally distributed. First, univariate associations between the outcome variable (HG and Non-NVP group) and personal history of nausea (motion sickness, seasickness, migraine, other headache, after anesthesia, contraception, and other situations) and NVP in relatives were studied using logistic regression analysis. Second, we adjusted the results for age, parity, pre-pregnancy BMI, marital status, and smoking. Because none of the women who had affected second-degree relatives were smokers, smoking could not be used in the adjustment analysis concerning second-degree relatives. Subsequently, a multivariable analysis (logistic regression analysis) was conducted including all history of nausea variables. To further investigate the associations between affected relatives and HG, an additional analysis on first-degree, second-degree, and both first- and second-degree relatives in both groups was carried out. The results are reported using odds ratios (OR) with 95% confidence intervals (CI). A significance level of $p=0.05$ (two-sided) was used. SAS Institute Inc. version 9.4. for Windows was used to perform the statistical analysis.

2.2 | Ethics statement

The study was approved by the Joint Ethics Committees of University of Turku and Turku University Central Hospital, Turku,

TABLE 1 Basic characteristics.

	Non-NVP group ($n=138$)			HG group ($n=102$)			
	n	Mean ± SD or % (*n*)	Range	*n*	Mean ± SD or % (*n*)	Range	*p*
Age (years)	138	30.2 ± 4.6	18.9–42.7	102	29.5 ± 5.0	18.6–42.8	0.226
Parity	134			102			0.025
Nulliparous		57.5 (77)			42.2 (43)		
Multiparous		42.5 (57)			57.8 (59)		
BMI[a] (kg/m^2)	134	23.4 (21.3–27.7)[a]	16.7–43.7	100	23.6 (21.0–28.2)[a]	18.0–40.6	0.799
Smoking	133			99			0.022
Non-smokers		87.2 (116)			96.0 (95)		
Smokers		12.8 (17)			4.0 (4)		
Marital status	134			101			0.178
Cohabited		97.8 (131)			94.1 (95)		
Single		2.2 (3)			5.9 (6)		
PUQE score[b]	138	3 (138)	0	100	11.0 ± 2.6	3–15	–

Note: Two-sample *t* test (age), Fisher's exact test (parity, marital status), Mann–Whitney *U* test (BMI) and chi-squared test (smoking) were used.

Abbreviations: BMI, body mass index; HG, hyperemesis gravidarum; NVP, nausea and vomiting of pregnancy; PUQE, Pregnancy-Unique Quantification of Emesis; SD, standard deviation.

[a]BMI reported using median and interquartile range.

[b]PUQE score ranges from 3–15, where 3 indicates no NVP (Koren et al. 2005). PUQE score in the HG group was assessed at the beginning of hospitalization.

Finland (43/180/2011 and 60/180/2011) on May 23, 2011. Participants in both the HG and Control groups received oral and written information about the study. Filling in the questionnaire was considered as informed consent. Participation in the study was voluntary.

3 | RESULTS

Personal history of nausea was more common among women in the HG group than among women in the Non-NVP group. Motion sickness (56.0%; $n=51$) and migraine (44.6%; $n=41$) were the most common nausea conditions in the HG group, whereas in the Non-NVP group motion sickness (24.8%; $n=33$) and other headache (25.4%; $n=33$) were the most frequent. Nausea during the use of contraception was infrequent in both groups. Nausea in other situations was specified with open question including in the HG group amusement park ($n=3$), labor ($n=3$), hunger ($n=2$), strong odors ($n=1$), and tiredness ($n=1$) and in the Non-NVP group with menstruation ($n=4$), gastroenteritis ($n=5$), moving car ($n=1$), hunger ($n=1$), and amusement park ($n=1$). The percentages are counted as the number of affirmative responses divided by the total number of responses in each question. (Table 2).

In univariate analysis, the women with history of motion sickness, sea sickness, migraine, other headache, and nausea in other situations were more likely to belong to the HG group, whereas no associations between nausea after anesthesia or during the use of contraception and HG were found. After adjusting the results by age, parity, pre-pregnancy BMI, marital status, and smoking, we found associations between HG and motion sickness, sea sickness, migraine, and nausea in other situations. In multivariable analysis with all history of nausea variables, having a history of motion sickness ($p=0.009$) and nausea with migraine ($p=0.005$) were associated with the HG group. (Table 2).

In the HG group, 59.1% ($n=55$) of women and in the Non-NVP group 28.0% ($n=37$) of women had relatives with a history of NVP. In both the HG group and the Non-NVP group, most of the affected relatives were first-degree relatives (94.6% [$n=52$] in the HG group and 97.2% [$n=36$] in the Non-NVP group, respectively), and having an affected second-degree relative was rare in both groups (5.5% [$n=3$] and 2.7% [$n=1$], respectively). In the HG group, 23.7% ($n=22$) of women had no affected relatives and 17.2% ($n=16$) were not aware of affected relatives (the response "I do not know"). In the Non-NVP group, 32.6% ($n=43$) were not aware of affected relatives.

In univariate analysis, the women in the HG group were more likely to have both any affected relatives ($p<0.0002$) and affected first-degree relatives ($p<0.0006$). After adjusting by age, parity, pre-pregnancy BMI, marital status, and smoking, the results remained the same. Having affected second-degree relatives was not associated with HG in either univariate or adjusted univariate analysis. The results are shown in Table 3.

TABLE 2 Associations between hyperemesis gravidarum and history of nausea.

Personal history of nausea	Non-NVP group ($n=138$)		HG group ($n=102$)						
				Univariate		Multivariable			
	% (n)	OR	% (n)	OR[a] (95% CI)	aOR[b] (95% CI)	OR[c] (95% CI)	p^a	p^b	p^c
Motion sickness	24.8 (33/133)	1	56.0 (51/91)	3.86 (2.18–6.84)	5.24 (2.67–10.31)	2.76 (1.29–5.89)	<0.0001	<0.0001	0.0086
Seasickness	14.6 (19/130)	1	39.6 (36/91)	3.82 (2.01–7.27)	4.82 (2.32–10.03)	1.77 (0.74–4.26)	<0.0001	<0.0001	0.202
Migraine	19.4 (26/134)	1	44.6 (41/92)	3.34 (1.84–6.05)	3.00 (1.58–5.70)	3.10 (1.40–6.86)	<0.0001	0.0008	0.0053
Other headache	25.4 (33/130)	1	41.3 (38/92)	2.07 (1.17–3.67)	1.81 (0.96–3.40)	1.33 (0.63–2.81)	0.013	0.066	0.456
After anesthesia	9.4 (12/128)	1	17.2 (15/87)	2.01 (0.89–4.55)	2.14 (0.89–5.14)	1.05 (0.37–2.99)	0.092	0.090	0.924
Contraception	2.3 (3/128)	1	6.7 (6/86)	3.01 (0.73–12.4)	3.09 (0.71–13.5)	7.75 (0.74–81.2)	0.126	0.134	0.087
Other situations	11.9 (13/109)	1	25.3 (20/79)	2.50 (1.16–5.41)	2.65 (1.13–6.20)	2.02 (0.77–5.31)	0.020	0.025	0.155

Note: The percentages are counted as the number of affirmative responses divided by the total number of responses in each question.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HG, hyperemesis gravidarum; NVP, nausea and vomiting of pregnancy; OR, odds ratio.

[a]Univariate analysis (logistic regression analysis).

[b]Adjusted for age, parity, pre-pregnancy body mass index, marital status, and smoking.

[c]Multivariable analysis including all history of nausea variables (logistic regression analysis).

4 | DISCUSSION

Our findings confirmed our previous retrospective results of the association of severe NVP and a personal history of nausea. As the various nausea conditions are typically correlated, we conducted a multivariable analysis, where we found that especially women with pre-existing susceptibility for motion sickness and nausea connected with migraine were more likely to suffer from HG. Additionally, a history of NVP in relatives was associated with HG. Our results suggest that different conditions involving nausea are likely to share parallel characteristics with HG and so may stem from similar backgrounds. This finding is significant in recognition of the risk factors for HG.

The etiology of motion sickness is generally accepted to arise from neurosensory conflict between visual and proprioceptive stimuli.[9] Motion sickness is known to have emetogenic potential, and susceptibility for motion sickness is associated with postoperative nausea and vomiting.[9,10] Although there are few studies concerning the connection between HG and motion sickness, Gadsby et al. suggested an association between NVP and motion sickness,[20] which we also confirmed in our previous study.[17] In a US study by Mullin et al. they found that prolonged HG was associated with motion sickness,[21] and in another study, Tulmaç et al. showed that a subset of HG patients had disturbances in the vestibular system.[12] This suggests that the link between HG and motion sickness might relate to abnormalities in the vestibulo-ocular pathway, although these data were preliminary, so more research is warranted. In a study with self-reported cases of HG by Fejzo et al., 30% of women had motion sensitivity.[16] In our study, the occurrence of motion sickness in the HG group was almost twice as high, although differences in the study setting might partly explain the difference: in their study, 63% of the women were hospitalized, whereas in our study all the HG women were hospital patients and therefore possibly suffering from more severe HG. Furthermore, all our patients were diagnosed by a healthcare professional, whereas 84% of the women in Fejzo's et al. were diagnosed with HG. Hence, the association of motion sickness might be mainly explained with the severity of the disease. In our study, HG was associated both with a history of motion sickness and seasickness in univariate analysis, but probably because of the close connection between these types of nausea, the association with seasickness lost the statistical significance in multivariable analysis.

Although the underlying reasons for the female predominance of migraine are not fully understood, female sex hormones undoubtedly play an important role in the pathophysiology.[22,23] Estrogen receptors are expressed in the central nervous system during migraine pain and fluctuations in the female sex hormones and differences in their receptor binding are known to have an impact on migraine attacks.[24] In our study, women with a history of migraine were more likely to have HG. In a study by Heinrich et al., among 16 women with HG, five had a history of migraine. Conversely, of 37 women who had a history of migraine, 10 had a history of HG.[6] In our study, the percentage of HG patients with a history of migraine was 7% higher than that of Heinrichs et al., but the small number of HG patients in their study might explain the difference. In our study, also 'other headache' was associated with HG in univariate analysis but lost the statistical significance after multivariable analysis, probably because of the similarity of these two conditions.

Nausea and vomiting have been reported as rare side effects of the use of oral contraception and emergency contraception.[11,25] The association with nausea as a side effect of contraception and HG is, however, not well documented. In a prospective study with 363 women by Gadsby et al., no connection between NVP and a history of nausea as a side effect of contraception was found.[20] In our previous study, women with a history of nausea with the use of contraception had higher odds for NVP, but this finding was lost in the multivariable analysis.[17] In the present study, we found no associations with a history of nausea with the use of contraception and HG. Admittedly, our population only included a few women suffering from nausea as a side effect for contraception and as a result our study may be underpowered to show the correlation. Also, the doses of hormones in modern contraceptives are low, and different forms of contraception might have different side effects; more research is needed in this field.

TABLE 3 Associations between hyperemesis gravidarum and history of nausea and vomiting of pregnancy in relatives.

	Non-NVP group ($n=138$)		HG ($n=102$)						
NVP in relatives	yes % (n)	OR	yes % (n)	OR[a]	95% CI	aOR[b]	95% CI	p^a	p^b
Any relative*	28.0 (37/132)	1	59.1 (55/93)	3.51	1.84–6.73	3.88	1.90–7.95	0.0002	0.0002
First degree relative	97.3 (36)	1	94.5 (52)	3.06	1.62–5.79	3.81	1.85–7.83	0.0006	0.0003
Second degree relative	2.7 (1)	1	5.5 (3)	3.57	0.36–35.03	3.25**	0.30–35.83	0.275	0.336**

Note: The percentages are counted as the number of affirmative responses divided by the total number of responses in each question.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HG, hyperemesis gravidarum; NVP, nausea and vomiting of pregnancy; OR, odds ratio.

[a]Univariate analysis (logistic regression analysis).

[b]Adjusted for age, parity, pre-pregnancy body mass index, marital status, and smoking.

*Responses: yes/no/not known (not known in Non-NVP group $n=43$, in HG group $n=16$).

**Because of no smokers in this group, smoking not included in the adjusted analysis.

Our results suggested that a family history of NVP, particularly in first-degree relatives, is associated with higher susceptibility for HG. Similar results have been reported in other studies,[15,17] and accordingly our study strengthens the evidence of a genetic component to HG. A twin study of 1725 women provided evidence that severe NVP might be highly heritable.[14] In a study by Fejzo et al., 28% of the HG patients had a mother with severe NVP or HG. Of those who had sisters with a pregnancy history, 19% of the sisters had HG. Furthermore, among women with the most severe symptoms, 25% had affected sisters.[16]

Allusion to familial aggravation of HG in previous studies has led to research on genetic regulation.[5] Perhaps the most convincing theory of genetic risk factors is centered on the role of growth/differentiation factor 15 (GDF15). Fejzo et al. have shown that genetic polymorphism in GDF15 was associated with HG in a large genome-wide association study.[26] High levels of GDF15 are produced in the placenta and the expression starts in early pregnancy.[5] There is also evidence of HG women having higher GDF15 levels.[27] In addition, alterations in the serotonin system have been linked to HG.[5] The serotonin system is important for motility and gastrointestinal tract functions and serotonin receptors can activate nausea and vomiting.[28] Stimulation of the 5-hydroxytryptamine-3 (5-HT3) receptor, which is encoded by an *HTR3C* gene variant, has been hypothesized to be a possible etiological factor at least in some HG cases.[5] Different types of 5-HT are involved in the pathophysiology of migraine as well.[29] Vomiting reflex is controlled in the area postrema, and 5-HT, neurokinin, dopaminergic, histaminergic, and muscarinic receptors are involved in the feedback mechanism. Histaminergic and muscarinic receptors are important in motion sickness in which the vestibular system is affected.[5] Furthermore, 5-HT3-receptor antagonists are widely used in treating nausea in general as well as HG and NVP in clinical practice. Coding and regulation of these receptors may at least partly explain our findings.

There are some limitations in our study. Our study groups were small, so the number of patients in subgroups of the most infrequent nausea variables and second degree relatives remained limited. However, studies on HG have been conducted in populations of similar or even smaller sizes.[3,6,12] The history of nausea was self-reported but assessed by a similar questionnaire in both groups. Also, women in the Non-NVP group self-reported having no NVP, which was not verified by a physician. Nevertheless, the diagnosis of no NVP is not typically assessed in medical records. Furthermore, to grade women not having NVP, a structured questionnaire, PUQE, was used. Our study also had several merits. It is one of the few to show the connection between the patient's own history of nausea and HG. Women in the HG group were diagnosed and hospitalized by a specialist in obstetrics and gynecology, which made the diagnosis reliable. Symptoms of NVP usually resolve by mid-pregnancy.[4] To avoid recall bias in the Non-NVP group, we included only women who participated by the end of week 20 of gestation. In both the HG and Non-NVP groups, the population was homogeneous and mainly Finnish, as reading and writing in Finnish was a presumption. This reduced any possible bias from ethnic differences that have been reported in literature.[2] Furthermore, women participating in the study were volunteers and were given no financial compensation. The women in the Non-NVP group were enrolled from the maternity healthcare clinics, which in Finland provide service free of charge, and the women in the HG group from a hospital. In Finland, hospitals are available for everyone independent of the financial situation or insurances because the hospital expenses are mainly covered by the taxation system, so the fees in the Finnish public healthcare system are very moderate for the patient.

5 | CONCLUSION

We conclude that HG is likely to stem from various factors, among which personal history of nausea, especially with motion sickness and migraine, are likely. Further, HG appears to have a hereditary predisposition, as it is more common in women with affected relatives. Recognition of risk factors for HG is valuable in pre-pregnancy patient guidance, providing tools for healthcare personnel to better help women. Also, early treatment of NVP symptoms is crucial especially with women susceptible for HG; our findings are usable for identifying women at risk of HG. Additionally, increasing knowledge about HG and its risk factors may serve to direct research and even advance development of specific treatments.

AUTHOR CONTRIBUTIONS

VSL is the principal investigator and author of the paper. PPK is the leader and co-author and contributed to study design and edited the manuscript. LML and JMAN contributed to study design, data collection and reviewing of the manuscript. MAK is the statistician of the study. All authors reviewed the manuscript and accepted the final version.

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CONFLICT OF INTEREST STATEMENT

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

DATA AVAILABILITY STATEMENT

The data sets generated and analyzed during the study are not publicly available for reasons of sensitivity (human data) but are available from the corresponding author on reasonable request. The authors confirm that all relevant data are included in the article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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