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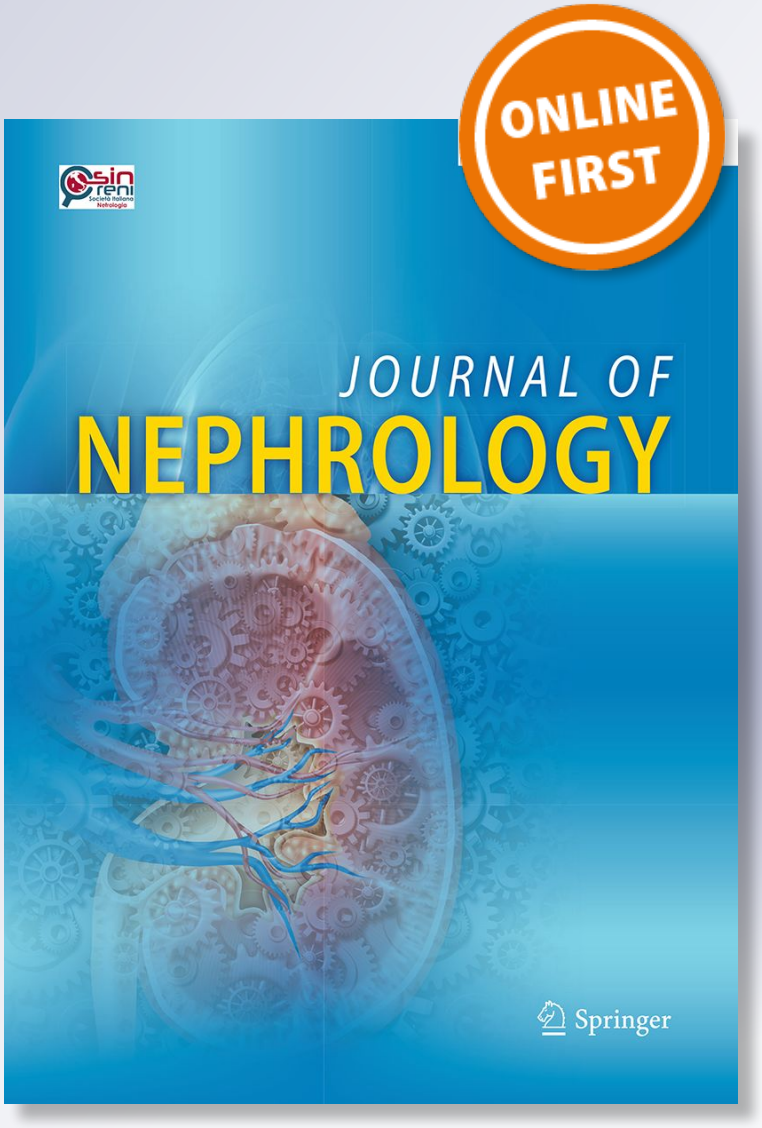

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ORIGINAL ARTICLE

Evaluation of inactive Matrix-Gla-Protein (MGP) as a biomarker for incident and recurrent kidney stones

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Abstract

Background Matrix-Gla-protein (MGP) is an inhibitor of vascular calcification. Its dephosphorylated and uncarboxylated inactive form, dpucMGP, is a marker of vitamin K status and of cardio-vascular outcomes in chronic kidney disease. We hypothesized that higher serum dpucMGP would be a biomarker of kidney stone disease.

Methods We measured serum dpucMGP in incident symptomatic kidney stone-formers and non-stone formers at a baseline visit. Symptomatic stone recurrence was assessed in the stones formers over a 5-year period. The association of dpucMGP with incident or recurrent kidney stones was assessed with and without adjustment for clinical, blood, and urine characteristics.

Results There was no significant difference in serum dpucMGP level between 498 stone formers and 395 non-stone former (510 vs 501 pmol/L; $p = 0.66$). In a multivariable model adjusting for clinical, blood and urine chemistries, higher MGP was associated with lower risk of stone formation (OR = 0.674, 95% CI 0.522–0.870), contrary to previous reports. Among 375 stone formers with 5 years of follow-up, 79 (21%) had symptomatic recurrence. No difference in serum dpucMGP was evident in recurrent versus non-recurrent stone-formers (482 vs 502 pmol/L; $p = 0.26$). Serum dpucMGP was correlated with cystatin C levels in non stone-formers, incident stone-formers and recurrent stone-formers ($r > 0.3$, $p < 0.0001$).

Conclusion Elevated serum dpucMGP was not associated with incident or recurrent symptomatic kidney stone events. However, higher level of dpucMGP was associated with lower risk of kidney stone in a multivariable logistic regression model.

Keywords Nephrolithiais · Matrix-Gla-protein · Biomarker · Cystatin C

Introduction

Matrix-Gla-protein (MGP) is a small endogenous protein that inhibits vascular calcifications [1]. MGP is expressed in many tissues, including heart, bone, and kidney [2]. It contains five γ-carboxyglutamate amino-acid residues that require post-translational carboxylation to be activated. In addition to carboxylation, phosphorylation of the serine residues is important to MGP role in inhibition of calcifications. The inactive form of MGP is the dephosphorylated and uncarboxylated MGP (dpucMGP) [3, 4]. MGP inhibits calcification, and high dpucMGP levels have been associated with increased risk of vascular calcifications. Further, dpucMGP correlates with cardiovascular outcomes in patients with CKD and diabetes, as well as in healthy women [5–7].

MGP is expressed in the kidney, where it plays a potential role to inhibit crystallization. When exposed to calcium oxalate crystals, MGP expression was upregulated in NRK-52E

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tubular cells (in vitro) and in rat kidneys (in vivo) [8, 9]. Genetic studies have identified MGP gene polymorphisms that associate with nephrolithiasis in humans [10]. Only one study has investigated a possible association between human kidney stone risk and serum dpucMGP. Wei et al. reported that higher serum dpucMGP concentration was associated with a past medical history of kidney stones and with future incident or recurrent stones in the general population [11].

Thus, the aim of this study was to determine whether higher serum dpucMGP concentration is associated with incident (first-time) symptomatic kidney stones or is predictive of recurrent symptomatic kidney stones over a 5 year period.

Material and methods

Study population

We studied 498 incident (first-time) symptomatic kidney stone-formers and 395 matched non-stone formers who had a baseline study visit to collect and bank serum at Mayo Clinic in Minnesota and Florida (USA), as previously described [12]. Symptomatic stone events required both the presence of symptoms (pain or gross hematuria) and a confirmed stone (obstructing the ureter on imaging or a voided stone) in the medical records. This cohort has been enrolling since the 1st January 2009 and all participants signed informed consent for participation in the study. Among incident symptomatic stone formers, there were 375 with 5 years follow-up for symptomatic stone recurrence. Medical records and a survey were used to ascertain baseline comorbidities. The non-stone former cohort was recruited using local mailings and community flyers. Participants answered a survey during the visit about stone risk and other comorbidities. Non-stone formers were sampled to be matched on age and sex to the stone former cohort (both cohorts were predominately white). Both stone formers and non-stone formers were sampled from the local populations of the two sites of the Mayo Clinic.

Methods

All participants were prospectively recruited for the study during the same time period and samples were collected using the same protocol and stored in freezer. For this study, we measured dpucMGP from previously frozen EDTA serum obtained at the baseline visit using an automated method based on dual-antibody chemiluminescence using the inaKtif MGP kit for IDS-iSYS (IDS, Boldon, UK) at the University hospital of Liège (Belgium). The established CV of the test was < 5%. The lower limit of quantification was 300 pmol/L and the upper reference range 521 pmol/L (CI 513–550 pmol/L). The other laboratory parameters were previously assessed at the Mayo Clinic in Minnesota (USA) as previously described [12]. Serum creatinine was measured by standardized isotope dilution mass spectrometry traceable enzymatic assay (Roche), and serum cystatin C by particle-enhanced turbidimetric assay (Gentian AS). Blood and urine analytes including calcium, magnesium, phosphate, uric acid, chloride, potassium, sodium, citrate (enzymatic, citrate lyase) and oxalate (enzymatic, oxalate oxidase) were all measured on a Roche Cobas autoanalyzer using previously validated assays.

Statistical analysis

Univariate comparisons were performed with Fisher's Exact Test for binary data and Wilcoxon rank sum test for continuous data. Logistic regression was used to identify independent characteristics associated with incident stone formers (versus non-stone formers), and separately among stone former, independent characteristics associated with symptomatic recurrence in 5 years (versus not recurrence in 5 years). Backward and forward selection of variables for the multivariable regression analysis was limited to variables that were significant in unadjusted analysis. All analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics

This study is in accordance with the Declaration of Helsinki and has been approved by the Mayo Clinic Institutional Review Board.

Results

Stone formers versus non stone formers

A total of 498 stone-formers and 395 non stone-formers were analyzed. The demographics, blood, and urine parameters are compared between both groups and are shown in Table 1. In univariate comparison, there was no detectable difference in serum dpucMGP measurement between both groups (Fig. 1).

However, in a multivariable logistic regression analysis (both in a forward and backward procedure, entering all available covariates), we found that cases with higher serum dpucMGP were less likely to have kidney stones (OR = 0.674, with 95% CI of [0.522–0.870] for a 1 SD increment, p = 0.0024) (Table 2). Cystatin C was the most important parameter in this logistic regression model (OR = 2.25, 95% CI 1.77–2.85). In addition, in an intermediate model adjusting only for sex, race, age

Table 1 Demographics, blood and urine parameters of non stone-formers s and stone formers

	Non stone-formers	Kidney stone formers	p value
Number of subjects	395	498	
Biometrics			
Gender			
Males (n [%])	196 (49.6)	273 (54.8)	0.14
Race			
Caucasian (n [%])	347 (87.8)	482 (96.8)	< 0.0001
Age (y)	45.7 ± 14.7	48.2 ± 14.3	0.0086
Systolic blood pressure (mmHg)	117.5 ± 16.7	121.2 ± 21.2	0.004
Diastolic blood pressure (mmHg)	74.8 ± 15.8	76.7 ± 9.9	0.044
Height (cm)	171.9 ± 9.7	171.6 ± 10.0	0.71
Weight (kg)	82.7 ± 18.9	91.6 ± 23.6	< 0.0001
Body mass index (kg/m^2)	27.9 ± 5.6	31 ± 7.4	< 0.0001
Waist circumference (cm)	90.5 ± 15.2	101 ± 19.4	< 0.0001
Hip circumference (cm)	103.1 ± 12.2	110.6 ± 16.5	< 0.0001
Comorbidities (n [%])			
Relatives with stones	77 (19.6)	189 (39)	< 0.0001
Chronic kidney disease	0 (0)	4 (0.8)	0.13
Gout	9 (2.3)	25 (5.1)	0.036
Diabetes mellitus	31 (7.9)	60 (12.1)	0.045
Urinary infection	126 (32.1)	201 (40.9)	0.0077
Chronic diarrhea	21 (5.4)	56 (11.4)	0.0025
Weight loss surgery	12 (3.1)	27 (5.4)	0.10
Heat cramps	27 (7.0)	70 (14.2)	0.0007
Blood			
dpucMGP (pmol/L)	501 ± 155.3	510 ± 205.1	0.66
Creatinine (mg/dL)	0.82 ± 0.20	0.9 ± 0.45	0.0026
Cystatin C (mg/L)	0.74 ± 0.17	0.87 ± 0.22	< 0.0001
Calcium (mg/dL)	9.25 ± 0.64	9.37 ± 0.55	0.013
Uric acid (mg/dL)	5.05 ± 1.51	5.64 ± 1.42	< 0.0001
Phosphate (mg/dL)	3.41 ± 0.52	3.73 ± 1.89	0.25
Bicarbonate (mmol/L)	26.7 ± 2.15	26.1 ± 2.27	0.0003
24 h urine			
Calcium (mg/24 h)	159.4 ± 114.7	205.4 ± 124.4	< 0.0001
Chloride (mmol/24 h)	120.8 ± 97.0	129.1 ± 72.1	0.022
Citrate (mg/24 h)	581.2 ± 447.0	620.1 ± 382.4	0.11
Magnesium (mg/24 h)	94.2 ± 61.4	100.8 ± 51.8	0.0041
Oxalate (mmol/24 h)	0.28 ± 0.21	0.24 ± 0.17	< 0.0001
Phosphate (mg/24 h)	661.5 ± 560.2	738.9 ± 373.3	< 0.0001
Potassium (mmol/24 h)	53.9 ± 46.0	50.1 ± 24.7	0.88
Sodium (mmol/24 h)	131.6 ± 111.7	141.2 ± 75.5	0.013
Uric acid (mg/24 h)	450.8 ± 437.5	455.5 ± 224.0	0.12
Volume (mL)	1851.8 ± 1273.4	1770.7 ± 794.5	0.62
Creatinine (mg/24 h)	1095 ± 876.0	1159.5 ± 546.9	0.0034
Albumin (mg/24 h)	9.43 ± 107.9	14.47 ± 61.13	< 0.0001
pH	6.3 ± 0.58	6.1 ± 0.55	0.0003

dpucMGP dephosphorylated and uncarboxylated matrix-gla-protein

For unit conversion of dpucMGP from pmol/L into µg/L, divide by 94.299

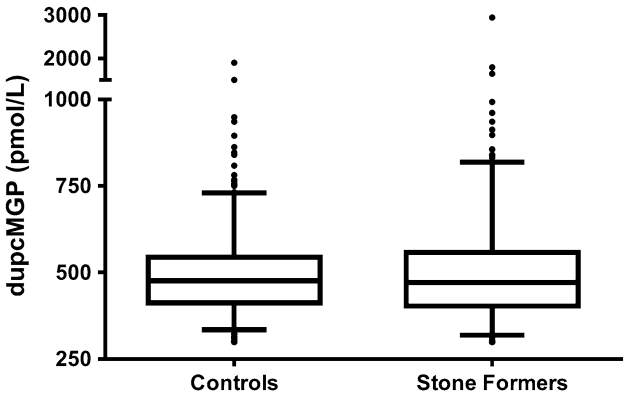

Fig. 1 Box plot of dpucMGP distribution in non stone-formers and stone formers. The dpucMGP median (Q1–Q3) was 475.8 (412.4–543.8) in non stone-formers and 471.2 (402.9–556.1) pmol/L in stone-formers. Dots represent < 5% and > 95% outliners

Table 2 ORs for 1 SD increment of the significant variables in the multivariable logistic regression model for incident kidney stone risk

	Odds ratio	95% CI
Body mass index	1.56	1.27–1.93
Race (other race vs Caucasian)	0.30	0.13–0.69
dpucMGP	0.67	0.522–0.87
Phosphate (blood)	1.45	1.09–1.93
Cystatin C (blood)	2.25	1.77–2.85
Potassium (urine)	0.50	0.35–0.71
Calcium (urine)	1.37	1.08–1.73
Phosphate (urine)	1.53	1.07–2.17
Oxalate (urine)	0.65	0.49–0.86
Relatives with stones (no vs yes)	0.38	0.26–0.56
Heat cramps (no vs yes)	0.42	0.24–0.76

dpucMGP Dephosphorylated and uncarboxylated matrix-gla-protein

and comorbidities, higher dpucMGP lower risk of kidney stones (OR = 0.47, 95% CI 0.35–0.62).

Recurrent versus non recurrent stone formers

Among the 498 stone formers, 375 had 5 years of follow-up to assess for symptomatic recurrence resulting in clinical care. Seventy-nine (21%) of the stone formers had at least one recurrence within the 5 year follow-up period. There was no difference in dpucMGP between recurrent and non-recurrent stone formers (483 vs 502 pmol/L, p = 0.26). In a multivariable logistic regression analysis adjusting for all other factors in Table 1, dpucMGP was not associated with symptomatic recurrence (OR = 1.102, 95% CI [0.671–1.809] for a 1 SD increment, p = 0.702).

Correlation

In addition, dpucMGP was significantly correlated (r > 0.25) with cystatin C levels in non stone-formers, incident kidney stone-formers and recurrent stone-formers (Table 3). It was also associated with the age of patients at the inclusion of the study in non stone-formers and recurrent stone-formers, while not in incident stone-formers. Serum dpucMGP levels didn't correlate with any other serum or urine parameters.

Discussion

In this prospective study, we found that dpucMGP levels were not associated with either incident symptomatic kidney stones or recurrent symptomatic stones over a 5 year period among incident stone formers. Thus, these data did not support a role of dpucMGP in the biology of kidney stone formation.

In contrast, several in vitro studies have shown that NRK-52 and MDCK renal tubular cells exposed to calcium oxalate crystals had an increase of MGP expression [8, 13]. Similarly, the kidney of hyperoxaluric rats fed with hydroxyl-L-proline or ethylene glycol had higher expression of MGP [9, 13–16]. However, a high concentration of calcium suppressed the expression of MGP in NRK-52 cells [17]. Yet, these studies assessed MGP expression by PCR or Western blot in renal cells, and thus may not correlate with serum dpucMGP levels. Indeed, we assessed serum dpucMGP in the present study which is dependent on vitamin K activation [18].

Goiko et al. have synthesized different segments of human MGP that were phosphorylated, γ-carboxylated, post-translationally modified or non-modified forms. Some of them selectively inhibited the growth of hydroxyapatite or calcium oxalate monohydrate crystals while promoting at the same time the growth of calcium oxalate dihydrate crystals [19]. Thus, different post-translationally modified MGP forms may play different roles according to crystal nature. As previously reported, about 94% of kidney stones with a known composition in the community are hydroxyapatite or calcium oxalate [20].

So far, there are few papers about MGP in stone-formers. One genetic variant of MGP, rs4236, has been significantly associated with higher risk of nephrolithiasis in several Asian populations (Indian [21], Japanese [22] and Chinese [10]), as well as in a Belgian cohort [11]. In addition, Wei et al. also identified the polymorphs rs2430692 and rs2098435 that were associated to higher dpucMGP levels in stone formers [11]. Yet, the prevalence of the rs4236 variant is unknown in our American population.

One Chinese study showed a decreased expression of MGP mRNA in the renal papillary tissue of stone-formers

Table 3 Correlation coefficient of dpucMGP with other parameters

	dpucMGP					
	Non stone-formers		Stone-formers		Recurrent stone-formers	
	Correlation coefficient	p value	Correlation coefficient	p value	Correlation coefficient	p value
Number of stones	NA		0.11	0.093	– 0.094	0.51
Age at inclusion	0.31	< 0.0001	0.19	< 0.0001	0.27	0.015
24 h urine parameters						
pH	– 0.089	0.078	– 0.10	0.038	– 0.17	0.15
Sodium	– 0.11	0.023	– 0.024	0.63	– 0.079	0.50
Potassium	– 0.11	0.035	– 0.071	0.14	– 0.20	0.089
Calcium	– 0.13	0.011	– 0.15	0.0034	0.0080	0.95
Magnesium	– 0.089	0.079	– 0.077	0.12	– 0.023	0.84
Chloride	– 0.12	0.021	– 0.018	0.71	– 0.084	0.47
Phosphate	– 0.064	0.21	– 0.071	0.15	– 0.15	0.19
Citrate	– 0.12	0.013	– 0.14	0.0041	– 0.21	0.069
Oxalate	0.0042	0.93	0.062	0.20	– 0.089	0.44
Uric acid	– 0.16	0.0019	– 0.15	0.0017	– 0.14	0.24
Creatinine	– 0.088	0.081	– 0.071	0.15	– 0.16	0.16
Albumin	0.16	0.050	0.13	0.030	0.20	0.18
Volume	– 0.015	0.76	– 0.047	0.34	– 0.056	0.63
Serum parameters						
Calcium	– 0.094	0.062	– 0.023	0.66	– 0.092	0.43
Uric acid	0.10	0.045	0.13	0.0032	0.11	0.31
Creatinine	0.050	0.32	0.13	0.0051	0.098	0.38
Phosphate	– 0.092	0.070	– 0.087	0.059	0.0046	0.97
Bicarbonate	– 0.054	0.29	– 0.17	0.0002	– 0.054	0.63
Cystatin C	0.38	< 0.0001	0.30	< 0.0001	0.41	0.0001

dpucMGP Dephosphorylated and uncarboxylated matrix-gla-protein

All variables were log transformed for the correlation

compared to patients with renal cancer [23]. However, the expression level of MGP protein measured by Western blot was not significantly different between both groups.

In our study, there was no significant difference in serum dpucMGP level between incident symptomatic stone formers and non-stone former, or between recurrent and non recurrent SF. Higher level of dpucMGP was actually associated with lower risk of kidney stone in a multivariable logistic regression model (OR = 0.674; 95% CI 0.522–0.870; p = 0.0024), which differs from previous studies on prevalent stone formers. Until now, only Wei et al. directly assessed serum dpucMGP in humans [11]. They found that the risk of being a prevalent stone former to be 1.5 higher per doubling of dpucMGP level in a large Belgian population. They also found the risk of a subsequent stone (incident or recurrent) to be 2.2 higher per doubling of dpucMGP. On the contrary, we found that a doubling of dpucMGP was associated with a threefold decreased risk of incident nephrolithiasis in a multivariable logistic regression model (OR: 0.315; 95% CI 0.179–0.554, p < 0.0001). In our study, dpucMGP was not significant in the univariate logistic regression, but was found to be significant in a multivariable model. Since MGP is a new biomarker, it is difficult to know the relevant confounders. By fully considering all potential confounders in the model we avoided making prior assumptions.

The different findings may be explained by some differences in the studied populations. Wei's study had only 16 incident stone formers during follow up and they were combined with recurrence among prevalent stone formers during follow up. The current study compared a much larger sample of 498 incident stone formers to non stone-formers s and recurrence was assessed among incident stone formers rather than among prevalent stone formers. By studying incident stone formers, and recurrence in incident stone formers, the temporal relationship between dpucMGP levels and stone episodes is more clearly delineated. The overall dpucMGP levels in our American subjects were higher than in the Belgian population. Finally, considering that genetics may impact both dpucMGP levels and nephrolithiasis, there could be a selection bias in that the Wei study included mostly related subjects from the same families [11].

However, a similar finding was that higher dpucMGP was associated to higher creatinine levels and lower eGFR in Wei population, as it was slightly correlated to higher levels of cystatin C in our population ($r > 0.3$, $p < 0.0001$). Indeed, other recent publications demonstrated a correlation between dpucMGP and kidney function, leading to the hypotheses that kidney disease may lead to vitamin K deficiency or conversely, that vitamin K deficiency is a risk factor of kidney damage [24, 25]. As shown previously, stone formers have an increased cystatin C levels that may be associated with the risk of chronic kidney disease [12]. While no study has directly reported an association between vitamin K status and urolithiasis, it is well-known that higher vegetables intake decrease the risk of urolithiasis [26]. Because vitamin K is essentially found in green vegetables, it is possible that vitamin K may indirectly associate with dietary factors that affect stone risk. However, there is no report of increased risk of nephrolithiasis associated to vitamin K antagonist intake to our knowledge.

It would also be of interest to assess MGP directly in the urine, as it is where stone formation occurs, and where MGP could act in inhibiting crystal growth. The urine concentration of MGP is unknown in human or rats, but it has been demonstrated that MGP is expressed at the apical membrane of renal cells in rats [9]. Thus it will be of interest to develop an assay for MGP in urine to have further insight into stone formation mechanisms.

The main limitation of the current study is the absence of genetic testing in order to estimate the prevalence of rs4236 variant in this cohort, which is associated with higher serum dpucMGP concentrations, and higher kidney-stone risk [10, 11, 22]. The comorbidities we adjusted for in the analysis were based on a survey and patients may have been unaware of certain conditions or have recall bias; this may have caused residual confounding in the association between MGP and kidney stones.

Conclusion

There was no association between serum dpucMGP concentration and risk of incident or recurrent kidney stones in this study. This outcome differs from the only other study on dpucMGP in stone-formers. Thus, further studies are required to determine if serum dpucMGP can be used as a biomarker of nephrolithiasis risk. It would be of interest to evaluate dpucMGP in human urine, and in group of stone-formers with a higher number of recurrences.

Acknowledgements The authors would like to thanks IDS for providing the MGP reagents.

Compliance with ethical standards

Conflict of interest PD and EC declare honoraria of consultancy for IDS. The results presented in this paper have not been published previously in whole or part, except in abstract format.

Ethical approval This study is in accordance with the 1964 Declaration of Helsinki and has been approved by the Mayo Clinic Institutional Review Board (IRB:08–006541).

Informed consent Informed consent was obtained from all individual participants included in the study.

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