Oral ondansetron for paediatric gastroenteritis in primary care: a randomised controlled trial

INTRODUCTION
Acute gastroenteritis (AGE) is common in young children and, although it is typically self-limiting, severe dehydration is an important complication. Approximately 5% of all GP consultations with children in the Netherlands are for AGE. Among those seen in primary care, 8.1% are referred to specialist care and 8000 are admitted to the hospital each year. However, it is thought that many of these referrals and admissions can be avoided.

International guidelines recommend care as usual (CAU) with oral rehydration therapy (ORT) to prevent and treat dehydration in children. It has been shown that prescribing ORT with education can reduce hospital admission by up to 45%, yet it is still underused in primary care; indeed, only 4% of all children overall with AGE received ORT when the child predominantly presents with vomiting. National paediatrics guidelines mention persistent vomiting as a predictor of ORT failure in children who are dehydrated; as such, most GPs are less likely to prescribe ORT when the child predominantly presents with vomiting.

Ondansetron has been reported to be safe and effective at stopping vomiting, increasing ORT success, and reducing hospitalisation rates among children presenting with AGE in secondary care; however, the practical value of ondansetron for treating children with AGE in primary care is unknown. The authors aimed to conduct a pragmatic randomised controlled trial (RCT) to investigate the effect of ondansetron: added to CAU; compared with CAU alone; and on vomiting in children aged 6 months–6 years with AGE consulting out-of-hours primary care (OOH-PC) services.

METHOD
Study design
Participants were enrolled from December 2015 until January 2018 at three OOH-PC centres in the north of the Netherlands: one in Groningen, one in Zwolle, and one in Assen. A detailed description of the study design, recruitment strategy, outcomes, and discussion of the informed consent procedure are described elsewhere. This study started with a pilot (Dutch Trial Register reference number: NL4700) undertaken from December 2015 until October 2016 but, as a result of the low inclusion rate, the primary outcome was changed from ‘referrals’ to ‘vomiting’. In agreement with the Medical Ethics Review Committee of the University Medical Center Groningen, children included from the pilot were also included in the new trial and the RCT was approved.

Inclusion and exclusion criteria
Children considered to be at increased risk of dehydration were included if they met the following inclusion criteria:

- Age 6 months–6 years
- AGE diagnosed by a GP
- One reported episode of vomiting in the 24 hours before presentation
- 4 reported episodes of vomiting in the 24 hours before presentation
- ≥4 vomiting episodes within 4 hours before presentation
- ORT failure in children who are dehydrated; most GPs are less likely to prescribe ORT when the child predominantly presents with vomiting.

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How this fits in
Ondansetron was found to be effective at reducing vomiting in children with AGE in secondary care, but this effect has never been evaluated in primary care. Based on the findings of this study, ondansetron use is effective at dramatically reducing vomiting, seems safe, and is positively evaluated by parents when used to treat children aged ≤5 years with acute gastroenteritis (AGE). As such, ondansetron could be considered by GPs as an additional treatment in the management of dehydration due to AGE, when the child is predominantly vomiting. Future research should disentangle the key factors leading to hospital referrals and consider ways to administer oral rehydration therapy more effectively in primary care or at home.

Interventions
Control group: CAU. CAU comprised instructions to buy oral rehydration solution and how to use it, as described in the acute diarrhoea guideline of the Dutch College of General Practitioners:15 10 ml/kg compensation when at risk of dehydration (that is, all children) and 15 ml/kg for 4 hours if a GP assessed the patient as being dehydrated. The research assistant provided the parents the instructions with a patient folder containing the same information, discussed alarm symptoms, and advised them to contact the GP if there was no improvement or symptoms worsened.15

The intervention: CAU plus ondansetron. Children allocated to the intervention group received the CAU described above plus a single weight-based dose of oral ondansetron syrup (0.1 mg/kg), in accordance with the Dutch Pediatrics Formulary.18 If the child vomited within 15 min of administration, the same dose was repeated once, but a third dose was not given.

Outcomes
Parents completed diaries for 7 days. For the first 4 hours after presentation, they reported hourly; thereafter, they reported daily until 7 days after presentation. If parents did not consent from the second parent (in most cases they were at home).

After consent was gained, children were randomly allocated to one of two intervention groups at a ratio of 1:1. An online randomisation tool was used to generate the allocation sequence in direct response to participant inclusion by the research assistant; concealment was not an issue because allocation was only generated after randomisation. The allocation sequence was stratified by age (6–24 months or >24 months) and severity of dehydration (‘at risk’ for no alarm symptom or ‘dehydrated’ for ≥1 alarm symptom). Comparisons between groups were adjusted for these stratification factors.

Participants, parents, GPs, and research assistants were not blinded to the allocated treatment. Ondansetron has already been proven effective at reducing vomiting in blinded RCTs.16,17 In this pragmatic RCT, the authors specifically aimed to investigate the potential effect of implementing ondansetron in routine primary care; blinding participants would, in this case, result in outcomes not translatable to daily practice. The statistician performing the analyses was blinded to the treatment allocation by an independent researcher. The primary outcome was not known by parents and GPs.

Randomisation and blinding
Randomisation occurred after written informed consent was obtained from the consulting parent plus verbal informed consent from the second parent (in most cases they were at home).
return the diary after multiple requests, information about the primary outcome was collected by telephone.

**Primary outcome** The primary outcome was the proportion of children who continued vomiting in the first 4 hours after randomisation. This evaluation point was chosen because the circulating concentration of ondansetron is expected to reach 50% of its maximum serum level at 3 hours after oral dosing, meaning that direct effects on vomiting are unlikely beyond 4 hours. In addition, national guidelines recommend that GPs evaluate the effect of treatment on symptoms and assess the indications for referral in children with AGE by 4 hours after initial presentation.

**Secondary outcomes** The following outcomes were assessed up to 4 hours after randomisation:

- number of vomiting episodes per child;
- ORT intake (ml) per participant; and
- proportion of children who experienced ≥1 adverse event(s) related to ondansetron.

The following outcomes were assessed up to 7 days after randomisation:

- proportion of children referred to specialist care; and
- proportion of children admitted to hospital.

Finally, parental satisfaction with ondansetron therapy was assessed using a five-point Likert scale.

**Statistical methods**

**Sample size** Based on a systematic review, it was estimated that 85% of children in the CAU group and 64% of children in the intervention group would continue vomiting within 4 hours. It was calculated that 100 children per group were needed to achieve an alpha of 0.05 and a power of 0.90. To compensate for an expected loss to follow-up of 10%, the authors aimed to include 220 children. For the intention-to-treat (ITT) analysis, the authors were able to include 88 and 87 children in the intervention and control groups, respectively; therewith, the power remained >80% (sample size n = 166).

**Handling of missing data** Using logistic regression, the authors explored whether baseline characteristics were related to missing values relating to their outcomes. For all single outcomes, further inspection of frequencies and distribution of values gave no indication that the missing values were related to the true values themselves [that is, values were distributed as theoretically expected]. In addition, Little's Missing Completely at Random test was not statistically significant (P-value $\chi^2 0.76$); thus, it was assumed that the missing data were missing at random. Supplementary Table S1 gives an overview of the baseline characteristics of complete cases versus participants with missing values.

All available participant data were entered as predictors in multiple imputation: baseline characteristics, outcomes, and any available variables potentially related to outcomes. After analyses on 20 separate multiple imputed datasets, the results were pooled. In line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Consolidated Standards of Reporting Trials (CONSORT) guidelines, all analyses were also performed on cases with complete data only.

**Main analyses** Data were analysed on both an ITT and a per protocol (PP) basis. In addition, analyses were performed on both multiple imputed data and complete cases. It was assumed that the pooled estimates of ITT analyses on the multiple imputed data would be most reliable and, as such, these were considered the main analyses. All analyses were performed using IBM SPSS Statistics (version 25).

The ITT population consisted of all patients randomly allocated to one of the two treatment groups, regardless of whether they received, or adhered to, the allocated intervention. The only excluded participants were those who did not meet the inclusion criteria or met the exclusion criteria (that is, no informed consent of the second parent or retraction of informed consent).

The PP population consisted of the ITT population, but also excluded participants if they did not receive treatment, deviated from the protocol, or withdrew from the study.

**Primary and secondary outcome analyses** In all analyses, the treatment (intervention) group was the independent predictor. The primary outcome (continued vomiting) was evaluated by logistic regression, and because all included participants vomited at baseline, analyses were not adjusted for baseline status. The secondary outcome of the number of vomiting episodes was analysed with a log-linear negative binomial model. The secondary outcomes of summed millilitres of ORT intake and parental satisfaction were analysed with a Mann–Whitney U test. Other secondary outcomes — referred, ‘admitted’,
Sensitivity analyses were performed on the pre-specified primary and secondary outcome of number of vomiting episodes, excluding the first hour (that is, from 2–4 hours only).

**RESULTS**

**Study participants**

In total, 1061 participants aged 6 months–6 years who presented with vomiting at one of the three participating primary care OOH-PC centres were screened. Of these, 867 children were excluded: no diagnosis of AGE (n = 227) and not eligible because the intention was to include children at increased risk of dehydration (n = 395) were the most common reasons for exclusion. Of the remainder, 194 children were included and randomised, 97 of these each formed the CAU and intervention groups (Figure 1).

Sixteen cases were excluded because parents did not return their written informed consent forms, despite initially giving their oral informed consent, and three parents withdrew informed consent after randomisation. As such, data for 175 participants were available for ITT analysis. Seventeen children did not receive the allocated intervention and six were lost to follow-up, resulting in 152 participants available for the PP analyses (Figure 1).

Included participants had a median age of 1.5 years (range: 6 months–6 years), 50.3% were female, the median duration of vomiting before presentation was 2 days (range 0.8–9.0 days), and 71.3% had diarrhoea. There were no statistical differences in baseline characteristics between the CAU and the intervention groups in either the ITT (Table 1) or the PP (Supplementary Table S2) populations.

The most common risk factor was fever (24.9%) and the most common alarm symptom was no urine output for 24 hours (14.3%) (data not shown).

There was a wide range of missing data for the variables used in the composite measures (12%–49%); in total, 154 participants (88.0% of the 175 included children) provided all data needed for the primary outcome measure (Table 2).

**Outcomes**

The effect of ondansetron on continued vomiting and vomiting episodes. The pooled estimates of ITT analyses on the multiple imputed data were considered as the main analyses. Ondansetron decreased the proportion of children who continued vomiting within the first 4 hours after randomisation from 42.9% to 19.5% (Table 2). This corresponded with a relative risk of 0.60 (95% confidence interval [CI] = 0.45 to 0.81) and number needed to treat of four (odds ratio [OR] 0.37, 95% CI = 0.20 to 0.72). In the intervention and ‘adverse events’ — were evaluated with logistic regression.

**Sensitivity analyses.** Sensitivity analyses were performed on the pre-specified primary and secondary outcome of number of vomiting episodes, excluding the first hour (that is, from 2–4 hours only).

| Table 1. Baseline characteristics of the intention-to-treat population |
|---------------------------------|------------------|------------------|------------------|------------------|
| Baseline characteristic         | Valid, n        | All participants, n = 175 | Valid, n        | CAU, n = 88     | Valid, n        | Intervention, n = 87 |
| Age, years, median (IQR)        | 175 1.5 (0.9–2.1)| 88 1.5 (0.9–2.0)| 87 1.5 (0.9–2.2)| 175 1.5 (0.9–2.1)| 88 1.5 (0.9–2.2)| 87 1.5 (0.9–2.2)|
| Female, n (%)                   | 175 88 (50.3)    | 88 50 (56.8)      | 87 58 (66.7)     | 175 88 (50.3)    | 88 50 (56.8)      | 87 58 (66.7)     |
| Weight, kg, median (IQR)        | 169 11.0 (9.5–14.0) | 86 11.0 (9.4–14.0) | 83 12.0 (9.5–14.3) | 169 11.0 (9.5–14.0) | 86 11.0 (9.4–14.0) | 83 12.0 (9.5–14.3) |
| Duration of vomiting prior to presentation, days, median (IQR) | 174 2.0 (1.0–3.0) | 87 1.2 (1.0–2.0) | 87 2.0 (1.0–3.0) | 174 2.0 (1.0–3.0) | 87 1.2 (1.0–2.0) | 87 2.0 (1.0–3.0) |
| Frequency of vomiting in past 24 hours, median (IQR) | 171 5.0 (4.0–10.0) | 86 5.0 (4.0–10.0) | 85 6.0 (4.0–10.0) | 171 5.0 (4.0–10.0) | 86 5.0 (4.0–10.0) | 85 6.0 (4.0–10.0) |
| Diarrhoea present, n (%)        | 174 124 (71.3)   | 87 66 (75.9)      | 87 58 (66.7)     | 174 124 (71.3)   | 87 66 (75.9)      | 87 58 (66.7)     |
| Duration of diarrhoea prior to presentation, days, median (IQR) | 124 2.0 (1.0–3.0) | 66 1.0 (0.4–2.0) | 58 1.0 (0.0–3.0) | 124 2.0 (1.0–3.0) | 66 1.0 (0.4–2.0) | 58 1.0 (0.0–3.0) |
| Frequency of diarrhoea in past 24 hours, median (IQR) | 123 3.0 (2.0–5.0) | 66 2.0 (1.0–5.0) | 57 1.5 (0.0–4.0) | 123 3.0 (2.0–5.0) | 66 2.0 (1.0–5.0) | 57 1.5 (0.0–4.0) |
| Dehydration assessed at 0–100% by GP, median (IQR) | 170 20.0 (10.0–40.0) | 85 20.0 (10.0–40.0) | 85 20.0 (10.0–40.0) | 170 20.0 (10.0–40.0) | 85 20.0 (10.0–40.0) | 85 20.0 (10.0–40.0) |
| Use of concomitant medication, n (%) | 175 65 (37.1) | 88 35 (32.2) | 87 34 (39.1) | 175 65 (37.1) | 88 35 (32.2) | 87 34 (39.1) |
| Additional risk factors of dehydration, n (%) | 175 63 (36.0) | 88 33 (37.5) | 87 30 (34.5) | 175 63 (36.0) | 88 33 (37.5) | 87 30 (34.5) |
| ≥2                              | 175 63 (36.0) | 88 33 (37.5) | 87 30 (34.5) | 175 63 (36.0) | 88 33 (37.5) | 87 30 (34.5) |
| Alarm symptoms of severe dehydration, n (%) | 175 32 (18.3) | 88 15 (17.0) | 87 17 (19.5) | 175 32 (18.3) | 88 15 (17.0) | 87 17 (19.5) |
| ≥2                              | 175 21 (11.1) | 88 11 (11.1) | 87 11 (11.1) | 175 21 (11.1) | 88 11 (11.1) | 87 11 (11.1) |

*Numbers only presented for those participants with diarrhoea. *Risk factors assessed at baseline were: ≥6 watery stools or diarrhoea, fever, and reduced intake of liquid/food.

*Alarm symptoms assessed at baseline were: confused or decreased consciousness, bradycardia, weak peripheral heart beat pulsations, capillary refill time >4 seconds, skin pinch test >4 seconds, cold or marbled extremities, and no urine output in the previous 24 hours. CAU = care as usual; IQR = interquartile range.
The effect of ondansetron on ORT intake, referrals, and hospital admissions. Intake of ORT, number of referrals, and number of hospital admissions did not statistically significantly differ between treatment groups. In both treatment groups, the median ORT intake within 4 hours was 10 ml, referral occurred for 19.4% of all children, and most referred children (74.0%) were admitted to hospital (data not shown). Of all included children, 14.4% were admitted to hospital (Table 2).

Associated adverse events and parental satisfaction with ondansetron. Ondansetron did not increase the occurrence of adverse events. The median parental satisfaction with treatment after 1 week was statistically significantly higher in the intervention group 4.0 (interquartile range [IQR] 4.0–5.0) than in the CAU group 4.0 (IQR 3.0–4.0), respectively (P = 0.027) (Table 2).

Sensitivity analyses
In the sensitivity analysis, the effect of ondansetron on continued vomiting during the first 4 hours after randomisation remained statistically significant (OR 0.44, 95% CI = 0.23 to 0.87), but the number of vomiting episodes did not differ between treatment groups (IRR 0.62, 95% CI = 0.34 to 1.13) (data not shown).

DISCUSSION
Summary
One dose of ondansetron given in an OOH-PC setting decreased the proportion of participants with AGE who had persistent vomiting by 54.5% (decreased from 42.9% [n = 33/77] to 19.5% [n = 15/77]) = 54.5% (p = 0.027) (Table 2). Similar estimates were found when repeating the analysis in the PP population (Supplementary Table S3).

Strengths and limitations
The authors are aware of no other studies investigating the practical effectiveness of ondansetron on vomiting and other important treatment goals in children with AGE, when parents consult in an OOH-PC setting. Other strengths of this study are that nearly 600 GPs collaborated over a period of >2 years, and that it was possible to gather data about the reasons for exclusion. From these data, it becomes clear that the intention to select the subgroup of children who, at presentation, frequently vomited was fulfilled. In addition, the use of an hourly diary for the first 4 hours provided detailed and reliable data on the primary outcome.

Limitations of the study were that there was a wide range of missing values measures. Although no association was found between missing values and either treatment, the findings based on these secondary outcome measures should be interpreted with caution. It could also be seen as a limitation that participants — that is, parents and GPs — were not blinded for the intervention. Although it is disputable whether this would have been desirable in a pragmatic trial, the authors believe it did not influence the primary outcome measurement as the aim
was to investigate the potential effect of implementing ondansetron in routine primary care and the outcome assessors were blinded.

**Comparison with existing literature**

The finding that oral ondansetron reduces the incidence of vomiting and the proportion of vomiting episodes within 4 hours after presentation at an OOH-PC centre is consistent with results of other studies.\(^{1,22}\) The findings presented here also indicate that this effect of ondansetron on vomiting persisted over a 4-hour period.

In addition, the results indicate that a 0.1 mg/kg dose of ondansetron in primary care is at least comparably effective at inducing vomiting cessation as a higher dose given in the emergency department.\(^{13}\) Despite ORTs being prescribed for all children included by research assistants, the reported ORT intake was low in both treatment groups for the current study. Studies from emergency department settings indicate that ORT can have a success rate of 100% when prepared and administered by qualified and trained nurses directly after giving a dose of ondansetron.\(^13\)

It would be interesting to study alternatives to ORT that children can better tolerate or accept at home, such as diluted apple juice.\(^{24}\) However, for the CAU group, the guideline of the Dutch College of General Practitioners was followed,\(^{15}\) which does not include the use of apple juice.

There could be several reasons for the high referral rate among children with AGE and frequent vomiting; a plausible explanation may be that it reflects a lack of success with ORT at home. In the current study, the median intake of oral rehydration solution of 10 ml in 4 hours was considered ineffective for children at any age. Finding ways to improve ORT success at home seems to be key to rectifying this issue. In addition, because vomiting cessation did not lower referral rates, the decision to refer a child with AGE may have been influenced by considerations other than risk factors for dehydration and hydration status.

**Table 2. The effect of ondansetron on primary and secondary outcomes of the intention to treat population**

<table>
<thead>
<tr>
<th>Effect of ondansetron on primary and secondary outcomes</th>
<th>Valid, n</th>
<th>All participants, n = 175</th>
<th>CAU, n = 88</th>
<th>Intervention, n = 87</th>
<th>Valid, n</th>
<th>CAU, n = 88</th>
<th>Intervention, n = 87</th>
<th>CAU, n = 88</th>
<th>Intervention, n = 87</th>
<th>CAU, n = 88</th>
<th>Intervention, n = 87</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continued vomiting, hours 1-4, n(%)</td>
<td>154</td>
<td>48 (31.2)</td>
<td>77</td>
<td>33 (42.9)</td>
<td>77</td>
<td>15 (19.5)</td>
<td>154</td>
<td>0.37</td>
<td>(0.20 to 0.72)</td>
<td>0.32</td>
<td>(0.16 to 0.66)</td>
</tr>
<tr>
<td>Vomiting episodes, hours 1-4, median (range)(^a)</td>
<td>137</td>
<td>0.0 (0.0–6.0)</td>
<td>67</td>
<td>0.0 (0.0–6.0)</td>
<td>70</td>
<td>0.0 (0.0–5.0)</td>
<td>137</td>
<td>IRR 0.51</td>
<td>(0.29 to 0.88)</td>
<td>IR 0.44</td>
<td>(0.21 to 1.03)</td>
</tr>
<tr>
<td>Intake ORT, mL, median (IQR)</td>
<td>88</td>
<td>10.0 (0.0–100.0)</td>
<td>46</td>
<td>0.0 (0.0–72.0)</td>
<td>42</td>
<td>35.0 (0.0–180.0)</td>
<td>88</td>
<td>P = 0.522</td>
<td>(0.16 to 2.36)</td>
<td>P = 0.093</td>
<td>(0.45 to 2.36)</td>
</tr>
<tr>
<td>Referrals, n(%)</td>
<td>144</td>
<td>28 (19.4)</td>
<td>73</td>
<td>14 (19.2)</td>
<td>71</td>
<td>14 (19.7)</td>
<td>144</td>
<td>1.19</td>
<td>(0.40 to 3.55)</td>
<td>1.04</td>
<td>(0.45 to 2.36)</td>
</tr>
<tr>
<td>Hospital admissions, n(%)</td>
<td>132</td>
<td>19 (14.4)</td>
<td>73</td>
<td>10 (13.7)</td>
<td>59</td>
<td>9 (15.3)</td>
<td>132</td>
<td>1.80</td>
<td>(0.91 to 3.55)</td>
<td>1.13</td>
<td>(0.43 to 3.00)</td>
</tr>
<tr>
<td>Adverse events, n(%)</td>
<td>96</td>
<td>30 (31.3)</td>
<td>48</td>
<td>19 (39.6)</td>
<td>48</td>
<td>11 (22.9)</td>
<td>96</td>
<td>0.63</td>
<td>(0.34 to 1.17)</td>
<td>0.45</td>
<td>(0.19 to 1.10)</td>
</tr>
<tr>
<td>Serious adverse events, n(%)</td>
<td>91</td>
<td>6 (6.6)</td>
<td>46</td>
<td>4 (8.7)</td>
<td>45</td>
<td>2 (4.4)</td>
<td>91</td>
<td>0.83</td>
<td>(0.45 to 1.54)</td>
<td>0.49</td>
<td>(0.09 to 2.81)</td>
</tr>
<tr>
<td>Parental satisfaction, median (IQR)</td>
<td>107</td>
<td>4.0 (3.0–4.0)</td>
<td>53</td>
<td>4.0 (3.0–4.0)</td>
<td>54</td>
<td>4.0 (4.0–5.0)</td>
<td>107</td>
<td>P = 0.027</td>
<td>(0.16 to 2.36)</td>
<td>P = 0.013</td>
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</tr>
</tbody>
</table>

\(^a\)Complete range provided instead of IQR because data are heavily skewed (IQR = 0–0). \(^b\)Mann–Whitney U test. \(^c\)Adverse events: erythema, hiccups, and headache. \(^d\)Serious adverse events: spasms/convulsions and breathing problems. Bold = statistically significant difference. CAU = care as usual. IQR = interquartile range. IRR = incidence rate ratio. OR = odds ratio. ORT = oral rehydration therapy.
potential side-effects is still indicated when it is prescribed.

**Implications for practice and research**
In this study, ondansetron use was found to be effective, safe, and positively evaluated by parents when used to stop vomiting among children aged 6 months–6 years presenting in primary care with AGE and vomiting. As such, the authors advocate that ondansetron be considered an add-on treatment for use by GPs when managing dehydration due to AGE and frequent vomiting in primary care. However, the findings also show that ondansetron alone will not substantially affect ORT intake or reduce the high referral rate to specialised care. Future research should aim to disentangle the key factors leading to hospital referral for children with AGE. Research should also consider ways to administer ORT more effectively in primary care or at home, such as direct administration by nurses, better parental education, and the use of alternatives for ORT.

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**Ethical approval**
This study was conducted according to the principles of the Declaration of Helsinki, and in accordance with the Medical Research Involving Human Subject Act and other guidelines, regulations, and acts. The trial was approved by the Medical Ethical Committee of the University Medical Center Groningen and was registered in the Dutch Trial Register (reference: NL5830).

**Provenance**
Freely submitted; externally peer reviewed.

**Competing interests**
The authors have declared no competing interests.

**Contributors**
Irma J Bonvanie and Anouk AH Weghorst contributed equally as co-first authors; they are the primary investigators, and are responsible for analysis and drafting the manuscript.

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