BMJ Paediatrics Open

# Limited caffeine consumption as first-line treatment in managing primary monosymptomatic enuresis in children: how effective is it? A randomised clinical trial

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**To cite:** Rezakhaniha S, Rezakhaniha B, Siroosbakht S. Limited caffeine consumption as first-line treatment in managing primary monosymptomatic enuresis in children: how effective is it? A randomised clinical trial. *BMJ Paediatrics Open* 2023;**7**:e001899. doi:10.1136/bmjpo-2023-001899

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjpo-2023-001899).

Received 7 February 2023
Accepted 28 March 2023



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## ABSTRACT

**Objective** Evidence about the negative caffeine effect on enuresis in children remains understudied or poorly understood. The study aimed to investigate the effect of caffeine restriction on the improvement and severity of primary monosymptomatic nocturnal enuresis (PMNE).

**Design** Randomised clinical trial.

**Setting** Two referral hospitals in Tehran, Iran, from 2021 to 2023.

**Patients** Five hundred and thirty-four PMNE children aged 6–15 years (each group 267).

**Interventions** Amount of caffeine consumption was recorded by the feed frequency questionnaire and was estimated by Nutrition 4 software. Caffeine consumption per day in the intervention group was <30 mg, and in the control group, 80–110 mg. All children were asked to return 1 month later to check the recorded data. The ordinal logistic regression analysis was used to assay the effects of caffeine restriction on PMNE by relative risk (RR) at a 95% CI.

**Main outcome measures** The effect of limited caffeine consumption on the improvement and severity of PMNE.

**Results** The mean age of the intervention and control groups was 10.9±2.3 and 10.5±2.5 years, respectively. The mean number of bed-wetting before caffeine restriction in the intervention and control group was 3.5 (SD 1.7) times/week and 3.4 (SD 1.9) times/week (p=0.91) and 1 month after intervention were 2.3 (SD 1.8) times/week and 3.2 (SD 1.9) times/week, respectively (p=0.001). Caffeine restriction significantly reduced the severity of enuresis in the intervention group. Fifty-four children (20.2%) improved (dry at night) in caffeine restriction and 18 children (6.7%) in the control group with RR 0.615 at 95% CI 0.521 to 0.726, p=0.001. The caffeine restriction significantly reduced the enuresis in children with a number-needed-to-treat benefit 7.417. It means you must treat 7.417 PMNE children with caffeine limitation to improve one child with enuresis (become dry).

**Conclusion** Caffeine restriction can be helpful in reducing PMNE or its severity. Constructive limitation of caffeine is suggested as one of the first-line treatments in the management of PMNE.

**Trial registration number** IRCT20180401039167N3.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous findings about the relationship between caffeine and enuresis are inconclusive. The role of caffeine on the severity of primary monosymptomatic nocturnal enuresis (PMNE) has yet to be studied, and the effect of caffeine on PMNE is still controversial. Furthermore, limited studies have been performed on the effect of caffeine materials on urinary incontinence, but not specifically on PMNE. It seems essential to establish actual evidence about this issue in more detail.

### WHAT THIS STUDY ADDS

⇒ According to the finding of this study, caffeine restriction can help reduce PMNE or its severity. Constructive limitation of caffeine is suggested as one of the first-line treatments in the management of PMNE.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Although it is not recommended to have caffeine restriction for every child, it may be considered in cases resistant to treatment. Preliminary evidence according to the caffeine limitation and PMNE is accumulating, but a more comprehensive study is needed to clarify topics of uncertainty. This study was the initial way to define clues to the reasons for PMNE and its severity.

## BACKGROUND

Primary monosymptomatic nocturnal enuresis (PMNE) is the most common type of nocturnal enuresis (NE) in school-age children.[1 2] Multiple medications are effective in the treatment of PMNE, but behavioural interventions are the first-line modalities, such as void before sleeping, resolve constipation, decrease amounts of salt, and protein and fluid intake during dinner time, especially before bed.[3 4]

Caffeine has positive and negative effects on various human organs.[5] Regarding the effect of caffeine on the urinary system and increasing urine production, different results have been seen.[6] Some studies have shown that caffeine has diuretic properties and increases urine production, exacerbating incontinence.[7] On the other hand, Sun *et al*, in a meta-analysis study, showed no evidence of an association between caffeine and the risk of urinary incontinence.[8]

The negative caffeine effect on NE in children needs to be further studied.[9] Despite kids being one of the most caffeine consumers worldwide, limited studies have been conducted at this age.[10] The role of caffeine on the severity of PMNE has not been studied, and the effect of caffeine on PMNE is still controversial. Furthermore, limited studies have been performed on the effect of caffeine materials on urinary incontinence, but not specifically on PMNE.

## OBJECTIVES

The main aim of this study was to investigate the effect of caffeine restriction on the improvement and to reduce the severity of PMNE to suggest a proposal to build a new bridge for further behavioural studies.

## MATERIAL AND METHODS

### Study design and setting

This study was a randomised clinical trial with a parallel control group without blinding that was conducted in two tertiary referral hospitals in Tehran, Iran, from September 2021 to January 2023.

### Subjects

The participants were recruited by convenience sampling methods. One thousand one hundred and twelve children aged 6–15 years with bed-wetting that referred to referral enuresis clinics were eligible for the study. These children used a different amount of caffeinated material daily. A urologist and paediatrician evaluated all children. If they had PMNE according to the definition of the International Children's Continence Society (ICCS),[11] they would be enrolled in the research. Inclusion criteria were children aged 6–15 years, with only night-time bed-wetting, ≥2 bed-wetting/week, more than 3 weeks, primary (no dry more than 6 months), without other urinary tract symptoms, and normal ultrasound of the kidneys and urinary tract. Exclusion criteria were children with urinary tract infection, urological anomalies, spinal cord anomalies, neurogenic bladder, obstructive sleep apnoea, diabetes (insipidus and mellitus), children using diuretics and those with congenital heart diseases and heart failure. By using the formula, $n = \frac{2\left(Z1-\frac{\alpha}{2}+Z1-\beta\right)^2\sigma}{d^2}$, $\sigma = 2.52$, $\beta = 20\%$, $\alpha = 5\%$ and d=1, 199 subjects were considered for each group (total 398 children). With a drop-out of 20%, 478 children were considered for the study. There was no lost to follow-up and drop-outs. Finally, 534 subjects with PMNE (each group of 267 children) were enrolled in the study and analysed (figure 1).

The parents completed a dietary questionnaire including children's demographic information and caffeine consumption. The amount of caffeine consumption in children was recorded based on the feed frequency questionnaire (FFQ) (Shahid Beheshti University of Medical Sciences, Tehran, Iran, valid questionnaire for Iranian people). It was estimated by N4 software (nutrition 4, N-Squared computing, New Zealand, V.2.5.3). To collect the data, a table is set up to record the number of bed-wetting/week by the parents. Constipation was defined by ROME III criteria: at least two criteria, including faeces, straining, dry and hard faeces, and perception of incomplete defecation.[12]

Confounders were controlled in three ways: study participants' restriction, matching of groups and pooled data stratifications. The main confounders were excluded by precise attention to the inclusion and exclusion criteria (all subjects with PMNE without other urinary tract symptoms, abnormal ultrasound of the kidneys and urinary tract, urinary tract infection, urological anomalies, spinal cord anomalies, neurogenic bladder, obstructive sleep apnoea, diabetes, using diuretics and heart failure). Restricting the children to two groups with the age range of 6–15 years would minimise confounding variables. Furthermore, the other main and potential confounders were matched in two study groups (age, sex, body mass index, constipation, parents' education and enuresis history). For effect modification, pooled data were classified into stratified variables, and stratified data were analysed.

### Randomisation description

The randomisation method was simple randomisation with allocation concealment. The children's randomisation was done unbiasedly by a computer-generated randomisation number. A number was randomly selected on the table with closed eyes, and the direction of movement was downward. The children were randomly assigned to the control and intervention study groups by the random numbers table, one by one. Furthermore, we considered 'randomisation blinding' or 'allocation concealment' to decrease the selection bias. Trial participants were allocated into treatment groups so they could not exploit this knowledge.

### Training of participants and recruitment start date

The amount of caffeine contained in each substance was informed to the parents, and they were taught how to calculate the amount of daily caffeine consumption. In order to achieve the compliance of parents and children for the correct calculation of daily caffeine consumption, their reports for 1 week were checked (1-week training). After ensuring their correct performance, the participants started the study.

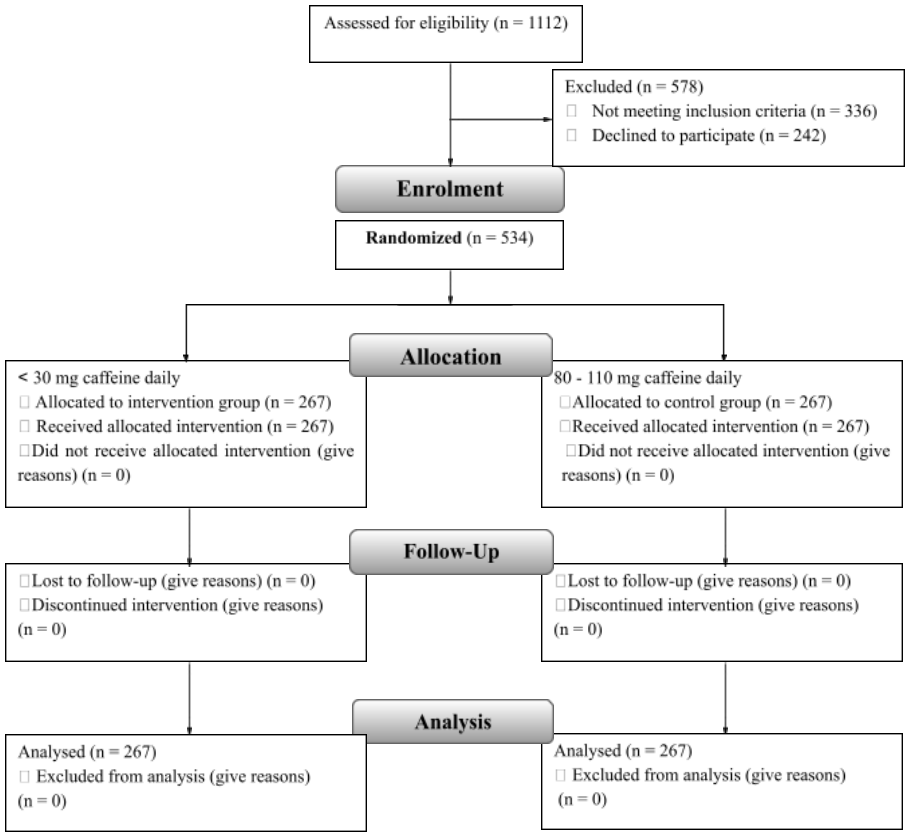


**Figure 1. Flow diagram of the study**

**Figure 1** Flow diagram of the study.

### Control group

In this group, the consumption of caffeinated foods included a glass of cocoa milk (100 cc cup contains 2–7 mg of caffeine) and 2–3 cocoa ice creams per week (weighing 75 g, each containing an average of 25 mg of caffeine) and 1–2 cups of tea (100 cc containing less than 50 mg caffeine) or coffee (75 cc contains 25–35 mg caffeine) or cappuccino (75 cc contains 30–40 mg caffeine) and 2–3 cans of cola per week (each 300 cc can contain 20–30 mg caffeine) and 1 chocolate a day (50 g each pack contains approximately 10 mg caffeine)) or a chocolate cake (weighing 100 g contains 5–7 mg caffeine) or a chocolate biscuit (weighing 100 g contains 4–6 mg caffeine).In the control group, the daily caffeine consumption limit was about 80–110 mg per day by N4 software and FFQ.

### Intervention group

The caffeine consumption limit per day in this group was less than 30 mg (one or two cups containing 100 cc of light tea, which was calculated by N4 software and FFQ). All children in this group were prevented from taking caffeinated materials such as cocoa milk, cocoa ice

creams, coffee, cappuccino, cans of cola, chocolate, chocolate cake and chocolate biscuit from the recruitment start date until 1 month later. Both groups were advised to urinate just before bed. All children were asked to return 1 month later to check the recorded data.

### Main outcome measures

The effect of limited caffeine consumption on the improvement (dry at night) of PMNE and its severity was studied as the main outcome measures. The severity of enuresis was defined as mild ≤2 times/week, moderate 3–4 times/week and severe ≥5 times/week.

### Statistical analyses

SPSS statistical software V.21 (SPSS) was used for data analyses. Quantitative data were expressed by mean and SDs and qualitative data by frequency and frequency per cent. The Kolmogorov-Smirnov test was used to test the normality of data distribution. The samples were with normal distribution. Group's data were compared by $\chi^2$ and t-test. The Spearman correlation test was used to investigate the relationship between the amount of caffeine and bed-wetting. Furthermore, ordinal logistic regression analysis was used to assay the effects of caffeine consumption restriction on the PMNE by OR at a 95% CI. P values <0.05 were defined as significant.

### Randomised clinical trial registration ID

This study was approved by the Iranian Randomised Clinical Trial registration office (ID: IRCT20180401039167N3; recruitment start date in the registration: 29 September 2021, Trial protocol available link: https://www.irct.ir/trial/58736. It was submitted as online supplemental file 1.

### Patient and public involvement

The results of this study will be provided as a bulletin to the academic paediatricians, primary care workers and participants' parents.

This article was edited by native editor. The certificate was submitted as online supplemental file 2.

## RESULTS

### Anthropometrics and basic variables of both groups

The mean age of the subjects was 10.7±2.3 years including 227 (42.5%) girls and 307 (57.5%) boys. Anthropometric parameters and other qualitative

**Table 1** Anthropometrics measures and basic qualitative data in caffeine restriction (N=267) and control group (N=267)*

| Anthropometrics measures | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Caffeine restriction | | | Control group | | | Overall | | | |
| | Min | Max | Mean±SD | Min | Max | Mean±SD | Min | Max | Mean±SD | P value |
| Age, years | 6 | 15 | 10.9±2.3 | 6 | 15 | 10.5±2.5 | 6 | 15 | 10.7±2.3 | 0.16 |
| Weight, kg | 30 | 91 | 54.3±14.8 | 30 | 88 | 53.1±15.5 | 30 | 91 | 53.7±14.9 | 0.28 |
| Height, cm | 123 | 166 | 146±12.2 | 123 | 166 | 145±12.3 | 123 | 166 | 145.6±12.2 | 0.3 |
| BMI, kg/m$^2$ | 15.2 | 34.2 | 25.2±5 | 13.6 | 35.1 | 24.9±5.1 | 13.6 | 35.1 | 25.1±5.1 | 0.58 |
| Stratified basic qualitative data (N, %) | | | | | | | | | | |
| | | | Caffeine restriction | | Control group | | Overall | | | |
| Sex | Girl | | 113 (42.3) | | 114 (42.7) | | 227 (42.5) | | | 0.93 |
| | Boy | | 154 (57.7) | | 153 (57.3) | | 307 (57.5) | | | |
| Constipation | No | | 199 (74.5) | | 193 (72.3) | | 392 (73.4) | | | 0.56 |
| | Yes | | 68 (25.5) | | 74 (27.7) | | 142 (26.6) | | | |
| Education, father | <diploma | | 48 (18) | | 46 (17.2) | | 94 (17.6) | | | 0.95 |
| | Diploma | | 134 (50.2) | | 133 (49.8) | | 267 (50) | | | |
| | >diploma | | 85 (31.8) | | 88 (33) | | 173 (32.4) | | | |
| Education, mother | <diploma | | 24 (9) | | 21 (8) | | 45 (8.4) | | | 0.52 |
| | Diploma | | 133 (49.8) | | 123 (46) | | 256 (47.9) | | | |
| | >diploma | | 110 (41.2) | | 123 (46) | | 233 (43.6) | | | |
| Parents' enuresis history | None | | 216 (80.9) | | 216 (80.9) | | 432 (80.9) | | | 0.41 |
| | Father | | 17 (6.4) | | 25 (9.4) | | 42 (7.9) | | | |
| | Mother | | 22 (8.2) | | 15 (5.6) | | 37 (6.9) | | | |
| | both | | 12 (4.5) | | 11 (4.1) | | 23 (4.3) | | | |

*Caffeine restriction and control groups were matched according to anthropometrics measures and basic qualitative characteristics (p>0.05).
BMI, body mass index; Max, maximum; Min, minimum.

Table 2 The effect of caffeine restriction in improvement PMNE 1 month after intervention

| Bed-wetting | Caffeine restriction, N (%) | Control group, N (%) | Regression coefficient (B) | RR 95% CI (lower-upper) | NNT | P value |
|---|---|---|---|---|---|---|
| Dry<br>enuresis | 54 (20.2)<br>213 (79.8) | 18 (6.7)<br>249 (93.3) | −1.25±0.288 | 0.615 (0.521 to 0.726) | 7.417 | 0.001 |

The caffeine restriction significantly reduced the enuresis in children. It seems that the probability of bed-wetting in the caffeine restriction group was about 14% lower than control group. Furthermore, a caffeine restriction had an NNT benefit 7.417; it means you have to treat 7.417 PMNE children with caffeine limitation to prevent one additional bad outcome as a child with enuresis become 'dry'.
N, number; NNT, number needed to treat; PMNE, primary monosymptomatic nocturnal enuresis; RR, relative risk.

information of both groups are shown in table 1. All pooled data were stratified to minimise confounders' effects, and stratum-specific parameters were analysed. The intervention and control groups were matched according to anthropometric measures and basic characteristics.

### The effect of caffeine restriction in the improvement of PMNE 1 month after intervention

According to the improvement of PMNE (dry night), 54 children (20.2%) improved in the caffeine restriction group, and in the control group, 18 children (6.7%) with relative risk (RR) 0.615 at 95% CI 0.521 to 0.726, p=0.001. The caffeine restriction significantly reduced enuresis in children. The probability of bed-wetting in the caffeine restriction group was about 14% lower than that in the control group. Furthermore, a caffeine restriction had a number-needed-to-treat benefit (NNT) of 7.417; it means that 7.417 PMNE children with caffeine limitation should be treated to prevent one additional bad outcome as a child with enuresis becoming 'dry' (table 2).

### The effect of caffeine restriction in reduction of PMNE severity 1 month after intervention

The mean number of bed-wetting before caffeine restriction in the intervention and control groups was 3.5 (SD 1.7) times/week and 3.4 (SD 1.9) times/week, respectively (p=0.91). Both groups were matched according to bed-wetting before intervention. After the intervention, the mean number of bed-wetting per week in the caffeine restriction and control groups was 2.3 (SD 1.8) times/week and 3.2 (SD 1.9) times/week, respectively (p=0.001).The severity frequency of enuresis (N, %) before intervention in the caffeine restriction group and control groups were: mild, 105 (39.3) and 100 (37.5); moderate, 60 (22.5) and 60 (22.5); and severe, 102 (38.2) and 107 (40), respectively (p=0.99). After the intervention, the severity frequency (N, %) of bed-wetting in caffeine restriction and control group were: no enuresis (dry), 54 (20.2) and 18 (6.7), mild, 101 (37.8) and 91 (34.1), moderate, 78 (29.2) and 75 (28.1), severe, 34 (12.7) and 83 (31.3), respectively (p=0.001). The restrictions on caffeine consumption significantly reduced severe enuresis in the intervention group (38.2% reduced to 12.7%). Furthermore, the rate of severe enuresis was significantly lower in the caffeine restriction group versus the control group (12.7% vs 31.3%) (table 3).

According to the effect of caffeine restriction on the severity of enuresis in the intervention group, severe versus mild enuresis had shown regression −0.997 with OR 0.369 at 95% CI 0.226 to 0.602, p=0.001. The severe enuresis was 63% lower than mild. Severe versus moderate enuresis had shown regression −0.932 with OR 0.394 at 95% CI 0.327 to 0.656, p=0.001. The severe enuresis was 60% lower than moderate. The moderate versus mild enuresis had shown regression −0.065 with OR 0.937 at 95% CI 0.613 to 1.43, p=0.764. Moderate enuresis was 6.3% lower than mild but insignificant (table 4). Caffeine restriction was significantly more effective in reducing severe and moderate enuresis than mild PMNE.

## DISCUSSION

This study aimed to evaluate the effect of caffeine restriction on the improvement and reducing the severity of bed-wetting as a first-line behavioural treatment in children with PMNE. The study showed that the frequency of dryness was significantly higher in the limited caffeine

Table 3 The frequency of PMNE severities in children before and after intervention in both groups

| Severity | Caffeine restriction, N (%) | Control group, N (% | P value |
|---|---|---|---|
| Before intervention | | | |
| Mild | 105 (39.3) | 100 (37.5) | 0.99 |
| Moderate | 60 (22.5) | 60 (22.5) | |
| Sever | 102 (38.2) | 107 (40) | |
| After intervention | | | |
| Dry | 54 (20.2) | 18 (6.7) | 0.001 |
| Mild | 101 (37.8) | 91 (34.1) | |
| Moderate | 78 (29.3) | 75 (28.1) | |
| Sever | 34 (12.7) | 83 (31.1) | |

The restrictions of caffeine consumption significantly reduced sever enuresis in intervention group (38.2% reduced to 12.7%). Furthermore, the rate of sever enuresis was significantly lower in caffeine restriction group versus control group (12.7% vs 31.3%).
N, number; PMNE, primary monosymptomatic nocturnal enuresis.

Table 4 The effect of caffeine restriction in severity of PMNE after intervention between severity slots

| Severity | Regression coefficient | OR 95% CI Lower–upper | P value |
|---|---|---|---|
| Sever/mild | −0.997 | 0.369 (0.226 to 0.602) | 0.001 |
| Sever/moderate | −0.932 | 0.394 (0.327 to 0.656) | 0.001 |
| Moderate/mild | −0.065 | 0.937 (0.613 to 1.43) | 0.764 |

It seems that caffeine restriction was significantly more effective in reducing sever and moderate enuresis compared with mild PMNE.
PMNE, primary monosymptomatic nocturnal enuresis.

consumption group than in the control group. It means that limited caffeine consumption was significantly effective in improving NE with NNT benefit 7.417. Furthermore, limited caffeine consumption decreased the severity of nocturnal enuresis in PMNE children.

According to ICCS recommendations, simple behavioural interventions (urotherapy) are the first-line strategies in treating NE, such as limited fluid intake in the evening, urination before sleep and limited caffeine intake. These modalities are effective alone, or in combination with other medications, although evidence regarding their efficacy is controversial.[11 13] However, many of these simple recommendations are not considered in treating children with enuresis. A descriptive-analytical study in Italy demonstrated that more than 90% of children did not advise dietary and other simple behavioural recommendations.[14] Our present study determined that caffeine limitation effectively treats PMNE with NNT 7.417.

Caffeine consumption is a common habit among adolescents and children. A mini-review found a positive correlation between age and caffeine utilisation.[15] Caffeine has positive and negative effects on multiple systems in the body.[16] While fluid intake is recognised to affect the severity of NE, the adverse effect of caffeine in PMNE needs to be better understood, and evidence from previous studies is mixed and contradictory.[17] A systematic review defined caffeine as associated with LUTS, mainly frequency, and urgency in women and men.[18]A cohort study showed that caffeine intake increased LUTS in adults (OR 2.09 at 95% CI 1.29 to 3.40).[19] Conversely, a cross-sectional study of 200 patients defined that caffeinated fluid did not affect urinary symptoms (OR 1.00, 95% CI 1.00 to 1.01).[20] These studies were not conducted in children and not especially in PMNE. Our study was conducted on children with PMNE. It showed that caffeine effectively decreased NE and the severity of bed-wetting.

Another cross-sectional study of 262 Chinese enuretic children aged 5–12 years demonstrated that children had more NE if they drank caffeinated beverages during the day.[21] Although the finding of this study was the same as our study, however, this study was conducted in PMNE in 534 children aged 6–15 years who received less than 30 mg and 80–110 mg of all caffeinated materials (beverages and nonbeverages) in 2 parallel randomised groups.

A study on 228 children aged 5–12 years defined that 52–109 mg daily caffeine intake was not correlated with the severity of enuresis.[22] Another study in Sweden twin suggested that coffee and tea had a limited effect on urinary incontinence.[23] However, a narrative review demonstrated that a high tea intake was positively associated with nocturia.[24] Another cross-sectional study that included 834 children aged 9±2 years showed that caffeine intake was significantly associated with PMNE.[25] Research about the effects of caffeine consumption on NE demonstrates confusing findings. Given existing evidence, lifestyle interventions and caffeine modification may have a significant and central role in the primary prevention of PMNE.

There is limited high-grade evidence to provide that caffeine may contribute to the pathogenesis of enuresis. A greater conception of the impact of caffeine on enuresis is needed to further improve the treatment of enuresis. Furthermore, associated pieces of evidence between LUTS and caffeine are sparse and often observational. Given the matter of these materials in daily life and their realised impact on the severity of PMNE, high-quality evidence is needed. A scoping review defined that caffeine reduction can reduce LUTS and NE. The studies were mainly observational, with a level of evidence 2–4 and a grade of recommendation B-C.[26] However, this study was randomised clinical trial research on children with PMNE.

Issues related to caffeine and the potential for the development and severity of PMNE remain to be clarified. Caffeine has multiple effects on various organs. It still is an interesting topic for further studies to develop and clarifies new therapeutic strategies. Although diverse health effects of caffeine have been expressed in children and adults, few data exist about caffeine consumption effects on PMNE in children. It is recommended that RCT studies with a larger population be conducted to obtain more objective evidence in the future. One of the limitations of this study was that the parents and participants did not believe to simple behavioural treatment. It is suggested to increase parents' perception of simple first-line strategies, such as reducing caffeine intake and fluid, by media and other social communities.

## CONCLUSION

According to the finding of this study, caffeine restriction can help reduce PMNE or its severity. Constructive limitation of caffeine is suggested as one of the first-line treatments in the management of PMNE. This study was the initial way to define clues to improving PMNE and severity.

**Acknowledgements** The authors appreciate the Iranian society of Pediatric and also urology and pediatrics department of Imam Reza and Golestan hospital and all members who assisted us in a way to complete this research.

**Contributors** Conceptualisation: BR and SS; formal analysis: BR and SR; investigation: BR and SS; methodology: BR and SR; writing—review and editing: SS and RB; writing—original draft: SS. All authors revised and approved the final version of this manuscript. SS is responsible for the overall content as the guarantor.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Consent obtained from parent(s)/guardian(s).

**Ethics approval** This study involves human participants and was approved by the ethics committee of Aja University of Medical Sciences approved research project of this study (Reg No: IR.AJAUMS.REC.1400.151). Link: https://ethics.research.ac.ir/form/rw0kykqzeg4r9v58.pdf. Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request.



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