

# BMJ Open Clinical characteristics and outcomes of hyponatraemia associated with oral water intake in adults: a systematic review

Gopala K Rangan,<sup>1,2</sup> Nilofar Dorani,<sup>1,3</sup> Miranda M Zhang,<sup>1,3</sup> Lara Abu-Zarour,<sup>1,3</sup> Ho Ching Lau,<sup>1,3</sup> Alexandra Munt ,<sup>1,2</sup> Ashley N Chandra,<sup>1,2</sup> Sayanthooran Saravanabavan,<sup>1</sup> Anna Rangan,<sup>4</sup> Jennifer Q J Zhang,<sup>1,2</sup> Martin Howell ,<sup>5</sup> Annette TY Wong<sup>1,2</sup>

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For numbered affiliations see end of article.

## Correspondence to

Dr Gopala K Rangan;  
[g.rangan@sydney.edu.au](mailto:g.rangan@sydney.edu.au)

## ABSTRACT

**Introduction** Excessive water intake is rarely associated with life-threatening hyponatraemia. The aim of this study was to determine the clinical characteristics and outcomes of hyponatraemia associated with excess water intake.

**Methods** This review was conducted using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. All studies (case reports, observational or interventional studies) reporting excess water intake and hyponatraemia in adults (1946–2019) were included.

**Results** A total of 2970 articles were identified and 177 were included (88.7% case reports), consisting of 590 patients. The mean age was 46±16 years (95% CI 44 to 48 years), 47% female, 52% had a chronic psychiatric disorder and 31% had no underlying condition. The median volume of water consumed and serum sodium at presentation was 8 L/day (95% CI 8.9 to 12.2 L/day) and 118 mmol/L (95% CI 116 to 118 mmol/L), respectively. The motivator for increased water consumption was psychogenic polydipsia (55%); iatrogenic (13%); exercise (12%); habitual/dipsogenic polydipsia (7%) and other reasons (13%). The clinical features on presentation were severe in 53% (seizures, coma); moderate in 35% (confusion, vomiting, agitation) and mild in 5% (dizziness, lethargy, cognitive deficit) and not reported in 5% of studies. Treatment was supportive in 41% of studies (fluid restriction, treatment of the underlying cause, emergency care), and isotonic and hypertonic saline was used in 18% and 28% of cases, respectively. Treatment-related complications included osmotic demyelination (3%) and rhabdomyolysis (7%), and death occurred in 13% of cases.

**Conclusion** Water intoxication is associated with significant morbidity and mortality and requires daily intake to substantially exceed population-based recommendations. The limitations of this analysis are the low quality and high risk of bias of the included studies.

**PROSPERO registration number** A pre-existing protocol in the international prospective register of systematic reviews was updated to incorporate any new amendments and reregistered at <http://www.crd.york.ac.uk/PROSPERO> (registration no. CRD42019129809).

## Strengths and limitations of this study

- Provides evidence on the potential dangers of overhydration.
- Reports the median volume of water consumed associated with water intoxication.
- Emphasises the importance of practitioners providing specific education when advising patients to increase water intake.
- Majority of studies (88.7%) were low quality, as they were derived from case reports/case series, and therefore, a high risk of bias.
- Water volume consumed and exposure time were self-reported or observed, reducing the precision of the estimate.

## INTRODUCTION

Self-induced water intoxication is a rare but serious complication of excessive fluid intake and the first case report was described in 1938.<sup>1 2</sup> It occurs when the oral intake of solute-free fluid per unit time exceeds the capacity of the kidney to excrete water (0.8–1.0 L per hour) leading to hypo-osmolar hyponatraemia.<sup>1 3–5</sup> The exact incidence of water intoxication in the general population is not known but suspected to be very rare due to the excretory capacity of the kidney.<sup>6</sup> In the defence forces, water intoxication occurred in 6.9 cases per 100 000 person-years (2001–2016)<sup>7</sup> but the prevalence may be as high as 5% (3.3–5.8%) in hospitalised psychiatric patients.<sup>8 9</sup> In the military, the incidence of water intoxication declined by 23.3% over the last decade due to education programmes.<sup>7</sup> The clinical manifestations of water intoxication depend on severity of hyponatraemia, and range from headaches, nausea, confusion, seizures and rarely death, due to cerebral oedema.<sup>3</sup>

In the published literature, multiple causes for water intoxication have been reported

and include situational circumstances (soldiers undertaking strenuous work in hot weather; athletes overhydrating during endurance exercise or other competitive events; iatrogenic polydipsia due to misinterpretation of medical advice; habitual/dipsogenic polydipsia, in which water drinking is perceived to have health benefits).<sup>10–13</sup>

In addition, chronic comorbidities (particularly schizophrenia spectrum disorders, beer potomania, low dietary solute intake), concomitant medications (neuroleptic drugs, thiazide diuretics),<sup>14</sup> recreational drug use (such as 3,4-methylenedioxymethamphetamine, MDMA)<sup>5 15–19</sup> and smoking<sup>20 21</sup> reduce the water volume required to cause intoxication by up to ~33% due to concurrent antidiuretic hormone release which impairs the renal capacity to excrete solute-free urine.<sup>5 17 19</sup> Other comorbid conditions and personal dietary habits, such as beer potomania and low dietary solute, also lower the threshold for water intoxication due to a decrease in obligatory urine volume required for urinary solute excretion.<sup>5 17 19 22</sup>

There has been long-standing interest on if there is an optimal amount of daily water intake required to maintain normal health span and prevent chronic disease.<sup>18 22 23</sup> Interestingly, a recent observational cohort study suggested that water intake may have a U-shaped relationship in the prevention of kidney disease progression.<sup>24</sup> Hence, clinical trials are in progress to prospectively evaluate the efficacy and safety of prescribed water intake for the secondary prevention of chronic diseases.<sup>25–27</sup> Whether recommending water intake in healthcare<sup>27</sup> or prescribing water intake in a clinical research trial it is important to understand the circumstances that could result in water intoxication.<sup>5 17</sup> Recently, a comprehensive narrative review on the pathogenesis of overhydration was published,<sup>28</sup> and therefore, the primary aim of this study was to perform a systematic review to determine the characteristics (demographics, comorbidities, volume of water consumed) associated with water intoxication. The secondary aims were to investigate the clinical features, treatment and outcomes.

## METHODS

### Protocol and registration

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>29</sup>

### Eligibility criteria

Studies were considered eligible if the following criteria were met: studies were case reports, observational cohort studies or randomised controlled trials; participants were humans aged 18 years and above and water intoxication was reported (table 1).<sup>30</sup> Studies were excluded if: they were review articles or editorial/discussion papers; they reported non-oral routes of water administration (eg, intravenous) or non-water induced hyponatraemia (eg, syndrome of inappropriate antidiuretic hormone); the serum sodium values were absent; or studies involved

**Table 1** Population, intervention, comparator and outcome characteristics of the inclusion criteria

Population	Adults with or without comorbid conditions with water intoxication
Intervention	Oral water intake
Comparator	No intervention
Outcomes	Clinical characteristics, volume of water intake, serum sodium levels, treatment and outcome
Setting	All
Study Design	Case reports, observational cohort studies or randomised controlled trials

children or animals. Studies that examined other beverage types (eg, soft drinks) were only included if they were reported in conjunction with plain water or incorporated within total fluid intake. All literature was restricted to English.

### Information sources and search strategy

The search strategy was developed by the authors (ND, MMZ, LA-Z and HCL) with input from an expert reference librarian. Relevant medical subject headings and keywords (such as ‘water intoxication’ and ‘hyponatraemia’; the full list of search terms is provided in online supplemental data file 1) were used to search databases (MEDLINE, EMBASE, Cochrane Library, Cochrane Database of Systematic Reviews and Cochrane Clinical Answers). Search strategies were developed for MEDLINE (OvidSP; 1946–2019), and adapted for EMBASE (OvidSP 1947–2019), CINAHL (EBSCO 1982–2019) and Cochrane Library (OvidSP 1991–2019) including CENTRAL, Cochrane Database of Systematic Reviews and Cochrane Clinical Answers. Additional hand-searches of relevant reference lists and supplementary journals were also conducted. All database searches were completed on 13 August 2019.

### Study selection

Search results from the databases were exported into EndNote V.X9 (Clarivate Analytics, USA) and duplicate records discarded. Titles and abstracts of all literature were screened to ensure relevance to the selection criteria, and any irrelevant articles were excluded. Full texts of the remaining articles were sourced and screened against inclusion and exclusion criteria in consultation with other researchers in the team (AW and GKR). Approved articles were subsequently incorporated into the systematic review, and reasons provided for excluded articles. The screening process was completed independently by two reviewers (ND and MMZ) which was further cross-checked by two coauthors (LA-Z and HCL).

### Data collection process and data items

A data extraction form was developed to incorporate the following information: author, year, study design, patient demographics (age, gender, country of origin);

comorbidity (chronic psychiatric condition (schizophrenia spectrum, bipolar, disorders, anxiety, obsessive-compulsive disorders, eating disorders), chronic medical disease (cardiovascular, kidney, liver, cancer, diabetes))<sup>31</sup>; reason for water consumption (psychogenic, habitual/dipsogenic, exercise-associated, iatrogenic, illicit drug use; urinary tract infection, competition-related polydipsia); concomitant medications (classified as either: no medication; medications associated with hyponatraemia; medications not associated with hyponatraemia<sup>14</sup>; volume consumed, sodium values (serum sodium, sodium levels in vitreous humour), symptom onset (acute: <48 hours; chronic: >48 hours); clinical features by severity (mild: either dizziness, light-headedness, nausea, headache; moderate: vomiting, confusion, agitation, dyspnoea, altered mental status; severe: seizures, coma, decorticate posturing, mydriasis)<sup>32</sup>; treatment types (supportive, isotonic or hypertonic saline), treatment-related complications (none, osmotic demyelination (OMD)) and outcomes (recovery, death). Data extraction and coding was performed by two authors (ND and MMZ), and verified by a third author (GKR).

### Quality assessment

The quality assessment of the selected studies was performed independently by two authors (ND and MMZ) and cross-checked by two coauthors (LA-Z and HCL) using a modified version of the Newcastle-Ottawa Scale (NOS) for cohort studies/case reports.<sup>33 34</sup> The scale assessed the standard four domains of the NOS (selection, ascertainment, causality and reporting) using eight questions to classify the selected literature as either 'low' (score of 0) or 'high' quality (score of 8). In the case of any disagreements, third reviewers were consulted (AW and GKR).

### Patient and public involvement statement

No patient involved.

### Data synthesis and analyses

Due to the heterogeneity of studies, a meta-analysis was not considered appropriate. The study results were summarised to outline the main outcomes of interest: age, gender, comorbidities (psychiatric, medical, none), concomitant medications (categorised by whether patients received one or more drugs that cause hyponatraemia); reason/s for water intake; volume of water consumed; clinical features (mild, moderate, severe) and onset; treatment types and complications, and outcomes. Data for water volume per unit time were divided into two groups consisting of an amount consumed per day (if the value reported for time was 1 day) or standardised to a 4-hour period (if the value for time was less than 1 day). Data from individual case reports were collected and mean values from aggregated data in case series or cohort studies. Descriptive statistics (mean, median, IQR and 95% CIs) were performed using JMP Pro statistics software (V.14, SAS Institute).

## RESULTS

### Study selection

The initial search revealed 2970 articles and after identifying duplicate records and screening title and abstracts, 1801 articles were excluded, leaving 310 full-text articles (figure 1). Of the 310 full-text articles screened for eligibility, 177 were included in the final synthesis.<sup>6 9–11 13 19 32 35–204</sup> The summary and full descriptions of all included studies and reasons for exclusion are provided in the online supplemental data files 2–4.

### Study characteristics

The 177 articles selected for inclusion contained data from a total of 590 patients, consisting of 223 individual case reports (n=119) and case series (n=24). The majority of the articles were case reports/case series (88.7%; n=157)<sup>6 10 11 13 32 35–41 43–52 55–70 73 74 76–78 80–84 86–88 91–103 105–119 121–129 131–135 137–161 163–165 167–193 195–204</sup> followed by retrospective cohort studies (n=10),<sup>9 53 75 85 90 104 120 136 194</sup> prospective cohort studies (n=5),<sup>42 54 71 89 166</sup> case-control studies (n=3),<sup>19 72 162</sup> a cross-sectional study (n=1)<sup>79</sup> and a prospective uncontrolled study (n=1)<sup>130</sup> (table 2).

### Quality of studies

The risk of bias assessment score based on the number of studies is summarised in table 3 and reported in more detail in online supplemental data file 5. The majority of studies (n=118; 66.7% of total) ranked as having a medium to high risk of bias.

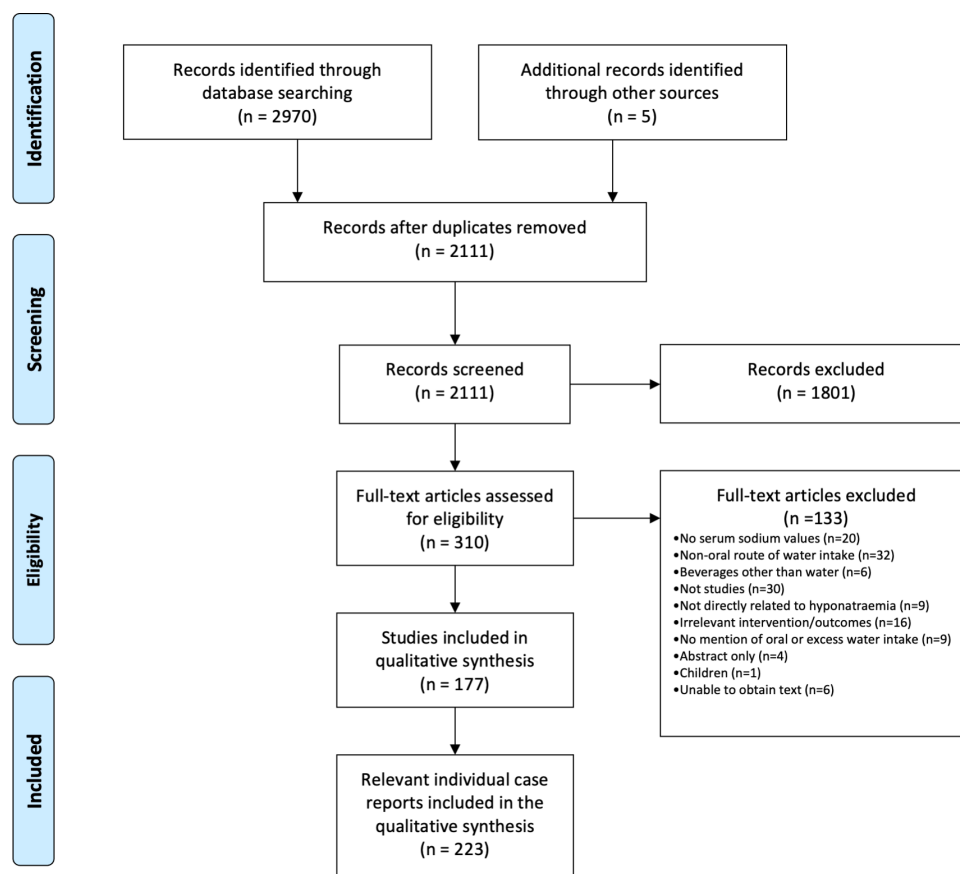
### Patient characteristics

#### Age, gender and country

Age was not reported for 25 patients (n=8 in individual case reports; one case series consisting of n=17 patients). In the remaining patients (n=565), the mean age was 46±16 years (mean±SD) (95% CI 44 to 48 years) (table 4). In patients with a specified gender (n=526), 47% were female and 53% were male. The majority of studies were from the USA (n=66; 37.3%), Japan (n=18; 10.2%), the UK (n=17; 9.6%), Israel (n=9; 5.1%) and Australia (n=8; 4.5%).

#### Comorbidities

The majority of patients suffered from a chronic psychiatric condition (52%), consisting predominantly of schizophrenia spectrum disorders and to a lesser extent others (bipolar, cognitive impairment, anxiety, personality and depressive disorders; dementia and anorexia nervosa) (table 4). Fifteen per cent patients suffered from an underlying chronic medical condition that led to the consumption of excess water (such as intractable hiccups, a urinary tract infection, dry mouth, low dietary solute) and/or exacerbated the risk for water intoxication. Approximately one-third of studies (31%) reported that patients had no underlying health condition (table 4). Data on smoking were missing in the majority (91.4%) of studies.



**Figure 1** PRISMA flow diagram outlining the literature selection process.

### Concomitant medications

Data for concomitant medications were not available in 31% of case reports/case series (table 4). In a quarter (23%) of case reports/case series patients were not taking any medications; another 41% were associated with exacerbating hyponatraemia<sup>14</sup> whereas the remainder (5%) were not taking medications that could contribute to lowering of the serum sodium (table 4). Of the former, the majority were antipsychotic drugs (68%), diuretics (13%), antidepressants (5%) and miscellaneous drugs (14%) (such as cyclophosphamide, carbamazepine, complementary medicines) (table 4).

### Volume of water consumed and serum sodium levels

#### Reasons for increased water consumption

In the majority, the cause was due to psychogenic polydipsia (55%) (mainly associated with the presence of schizophrenia spectrum disorder) (figure 2); 13% of causes were due to iatrogenic polydipsia where water intake was recommended on medical advice, such as preparation for an ultrasound; 12% of cases were associated with exercise; 7% of cases were due to habitual/dipsogenic polydipsia; 2% there were multiple reasons; and the remainder of cases (11%) included miscellaneous conditions [self-remedy for an infection (urinary tract infection, gastroenteritis, respiratory tract infection)]; avoidance of substance abuse through urine drug testing; intractable hiccups; involvement in a research

**Table 2** Characteristics of studies that met the inclusion criteria

Study design	No of articles n (%)	No of patients N (%)
Case reports	157 (88.7)	219 (37.1)
Retrospective cohort studies	10 (5.6)	254 (43.1)
Prospective cohort studies	5 (2.8)	44 (7.5)
Case-control studies	3 (1.7)	36 (6.1)
Cross-sectional study	1 (0.6)	27 (4.6)
Prospective uncontrolled study	1 (0.6)	10 (1.7)
Total	177 (100)	590 (100)



**Table 3** Risk of bias assessment

Score	No of publications	Risk of bias
1	0	High
2	5	High
3	20	Medium
4	53	Medium
5	40	Medium
6	15	Low
7	18	Low
8	26	Low

study or participation in a competition; use of illicit drugs such as MDMA; paruresis) (table 4).

#### Volume of water consumed

There was wide heterogeneity in the method of reporting the volume of water that was consumed. Of the 223 case reports/case series, quantitative data were provided in 56% (n=125/223), qualitative information alone in 40% (n=90/223) and no data was reported in 4% (8/223) (table 4). In addition, the quantitative data that was provided in the case reports/case series were either self-reported or estimated by observers of the patient (family, friends, medical staff). In cases that provided a quantitative

**Table 4** Summary of demographics, serum sodium and water intake volumes in the case reports/case series

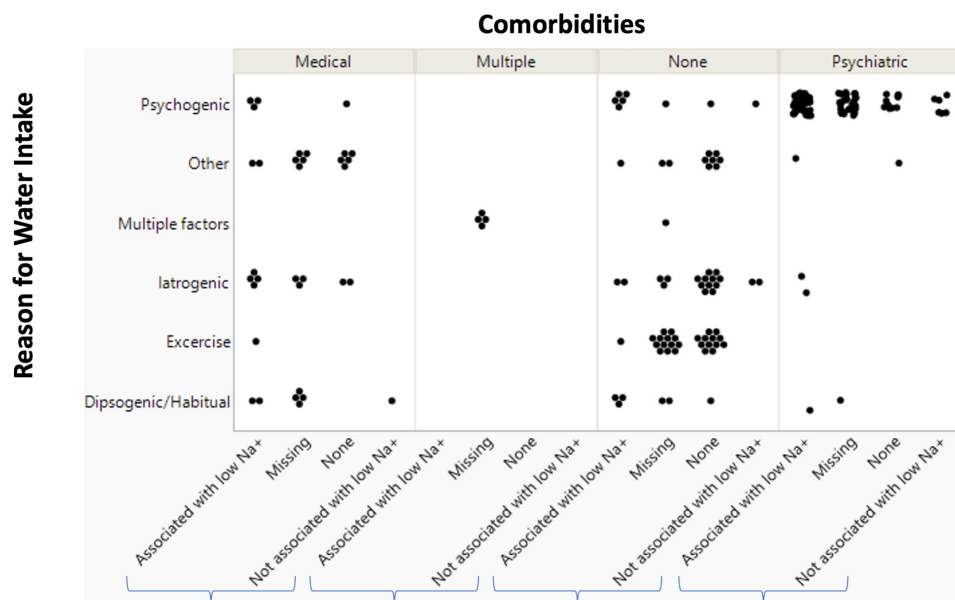
	All	Mild hyponatraemia (130–134 mmol/L)	Moderate hyponatraemia (125–129 mmol/L)	Severe hyponatraemia (<125 mmol/L)
Mean age (years) (95% CI)*	46±16 (43.6 to 48.0)	38±10 (30.3 to 45.0)	41 (35 to 47)	47 (45 to 49)
Male:female (%)†	53:47	67: 17	62: 38	52:48
Comorbidities (%)				
None	31% (69/223)	50% (5/10)	44% (12/27)	28% (52/186)
Medical condition	15% (33/223)	0% (0/10)	11% (3/27)	16% (30/186)
Psychiatric disorder	52% (117/223)	50% (5/10)	41% (11/27)	54% (101/186)
Both (medical +psychiatric)	2% (4/223)	0% (0/10)	4% (1/27)	2% (3/186)
Concomitant medications (%)				
Not reported	31% (70/223)	30% (3/10)	44% (12/27)	30% (55/186)
No medications	23% (51/223)	50% (5/10)	26% (7/27)	21% (39/186)
Associated with hyponatraemia	41% (92/223)	20% (2/10)	30% (8/27)	44% (82/186)
Not associated with hyponatraemia	5% (10/223)	0% (0/10)	0% (0/27)	5% (10/186)
Reason for water intake				
Exercise	12% (27/223)	50% (5/10)	29.6% (8/27)	8% (14/186)
Iatrogenic	13% (29/223)	0% (0/10)	18.5% (5/27)	13% (24/186)
Habitual/dipsogenic	7% (15/223)	0% (0/10)	11.1% (3/27)	6% (12/186)
Psychogenic	55% (123/223)	40% (4/10)	33.3% (9/27)	59% (110/186)
Multiple reasons	2% (5/223)	0% (0/10)	3.7% (1/27)	2% (4/186)
Other	11% (24/223)	10% (1/10)	3.7% (1/27)	12% (22/186)
Mean serum sodium (mmol/L) (95% CI)	118 (116 to 118)	132 (131 to 133)	127 (126 to 127)	114 (113 to 115)
Median water intake per day‡ (litres) (95% CI)	8.0 (8.9 to 12.2)	5.0 (–2.2 to 14.5)	8.0 (5.3 to 9.7)	9.0 (9.2 to 13.0)
Median water intake over 4-hour period (litres) (95% CI)§	5.3 (5.3 to 8.6)	3.1 (–0.3 to 8.3)	6.2 (3.3 to 9.1)	7.5 (5.4 to 9.6)

\*Age was not reported in n=25 individuals.

†Gender was not reported in n=64 individuals.

‡Data are from n=76 case report/case series.

§Data are from n=49 case report/case series.



**Figure 2** Categorisation of cases according to underlying comorbidities, main reason for water intake and use of concomitant drugs associated with hyponatraemia (low Na<sup>+</sup>).

value, it was estimated either as an amount consumed in a single day (n=76) or over hours (median 4 hours, range 0.5–23 hours; n=49). In studies that reported the volume over hours, the median intake of water was 5.3 L over a 4-hour period (95% CI 5.3 to 8.6 L). In studies that reported the volume in a single day, the median intake of water was 8.0 L over 24-hour period (95% CI 8.9 to 12.2 L) (table 4). In 90 cases/case series, only qualitative descriptions were provided to estimate water intake, and in 8 cases/case series no description was included. Of the qualitative studies, common terms to describe water intake included: ‘excessive water intake’ (n=29); ‘large amounts’ (n=18); ‘compulsive water intake’ (n=9); ‘copious quantities’ (n=5); ‘several litres per day’ (n=4); or ‘overhydration’ (n=4). Some examples of other terms that were used included: ‘always at the tap’ (n=1); ‘plenty of water’ (n=1); ‘frequent trips to the water fountain’ (n=1).

#### Serum sodium levels

The median serum sodium was 118 mmol/L (IQR: 111–123; range 83–134 mmol/L). In 6 of 40 fatal cases (29/223 studies), the median vitreous humour was 112 mmol/L (IQR: 103–116; range 92–117 mmol/L). Age, gender, the median water intake and reasons for water intake were similar in patients with mild, moderate or severe hyponatraemia (table 4). In addition, the scatterbox plot of the data suggested that patients with psychiatric conditions were predisposed to a lower serum sodium level than those with no underlying health problems (figure 3).

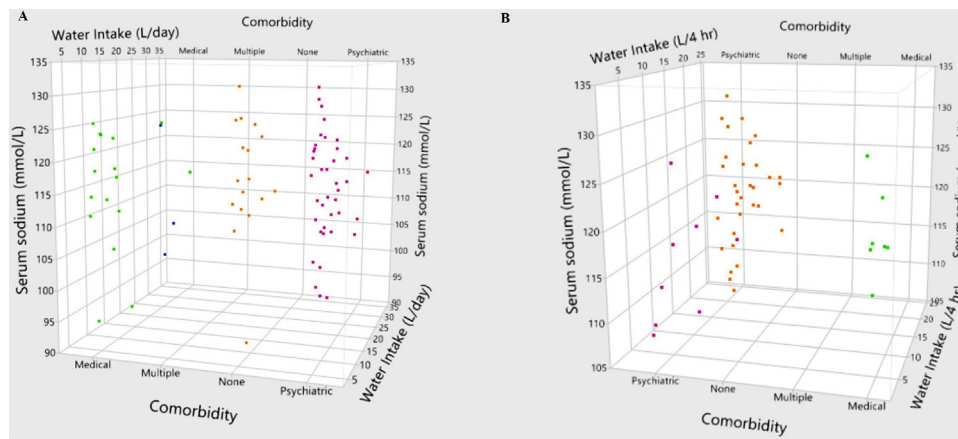
#### Clinical features and treatment of water intoxication

##### Clinical features

Clinical features were not reported in 4.5% of case reports/case series (table 5). In the remainder, 2.7% of patients reported no symptoms or signs; in 4.9% the clinical features were mild in severity (5/10: dizziness; 3/10: nausea; 1/10: lethargy; 1/10: cognitive deficit); in 34.5% the clinical features were moderate in severity (56/76: confusion; 13/77 vomiting; 5/77: dyspnoea; 2/77: agitation; 1/77: tremor); and in 53.4% the symptoms were severe (81/119: seizure; 38/119: coma) (table 5). The onset of clinical features was not reported in 30% of case reports/case series and in the remainder, the majority were acute (less than 48 hours; 41%) and chronic (greater than 48 hours; 26%) and 3% were asymptomatic (table 5).

##### Treatment and treatment-related complications

Treatment was not reported in 13% of case reports/case series (table 5). In the remainder, treatment was supportive care (41%; n=92) which included fluid restriction (48/92), antipsychotic drugs (14/92), behavioural therapy: (9/92), diuretics (3/92), emergency medical care (3/92), no treatment (12/92) or other (3/92). Twenty-eight and 18% of case reports/case series reported the use of 3% hypertonic saline and isotonic saline respectively which was administered in patients with severe hyponatraemia and/or depending on severity of clinical features (table 5 and figure 4). Ninety per cent of studies reported no treatment-related complications, but rhabdomyolysis and OMD syndrome occurred in 7% (n=16/223) and 3% (n=7/223) of case reports/case



**Figure 3** 3D scatterplot box to group cases according to water intake (A: litres per day; B: litres over 4 hours), comorbidity and serum sodium. Dots are coloured according to comorbidity group (psychiatric condition, pink; no underlying health condition or none, orange; multiple conditions, blue; medical condition, green). 3D, three dimensions.

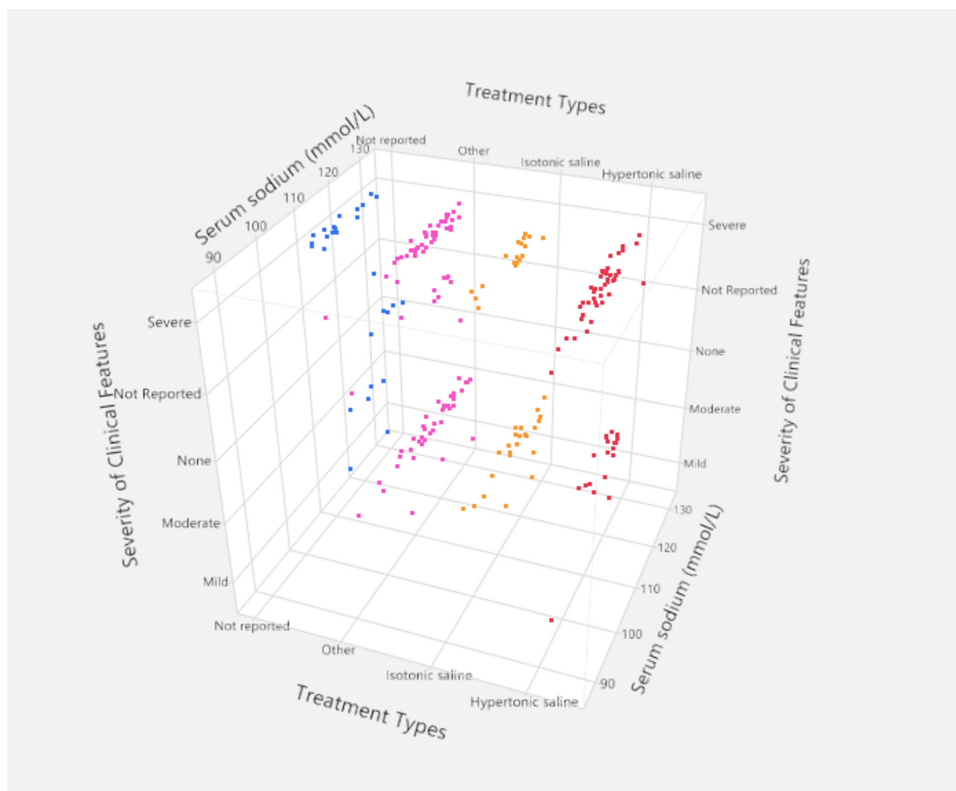
series, respectively (table 5). In the cases with rhabdomyolysis, the clinical presentation in 43% (7/16) included seizures.

**Outcomes**

The outcome was not reported in 9% of studies (table 5).

**Table 5** Clinical features, patterns of treatment and clinical outcomes of water intoxication

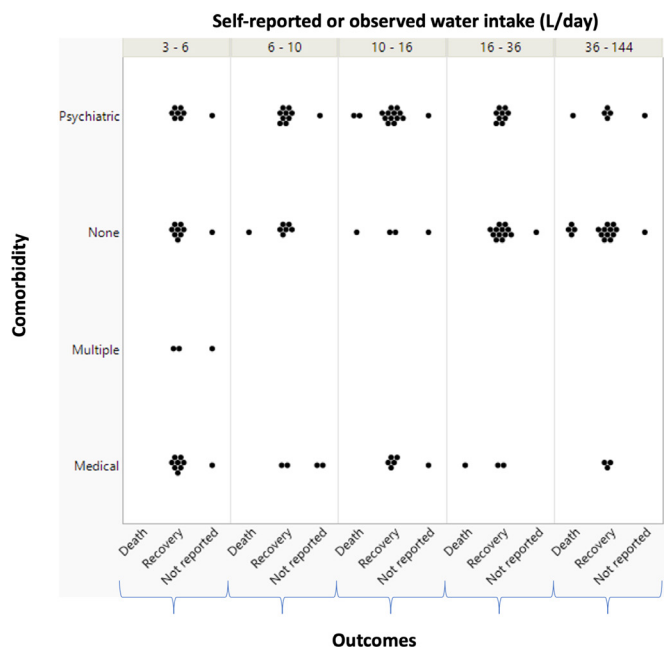
% (no/total data available)	All	Mild hyponatraemia (130–134 mmol/L)	Moderate hyponatraemia (125–129 mmol/L)	Severe hyponatraemia (<125 mmol/L)
<b>Clinical features</b>				
Not reported	4.5% (11/223)	10% (1/10)	15% (4/27)	3.2% (6/186)
No symptoms	2.7% (6/223)	40% (4/10)	4% (1/27)	0.5% (1/186)
Mild	4.9% (10/223)	10% (1/10)	7% (2/27)	3.8% (7/186)
Moderate	34.5 (77/223)	40% (4/10)	37% (10/27)	33.9% (63/186)
Severe	53.4% (119/223)	0% (0/10)	37% (10/27)	58.6% (109/186)
<b>Onset of clinical features</b>				
Not known	30% (67/223)	0% (0/10)	37% (10/27)	30.7% (57/186)
No clinical features reported/asymptomatic	3% (6/223)	40% (4/10)	4% (1/27)	0.5% (1/186)
Acute (<48 hours)	41% (92/223)	30% (3/10)	41% (11/27)	41.9% (78/186)
Chronic (>48 hours)	26% (58/223)	40% (4/10)	18% (5/27)	26.9% (50/186)
<b>Treatment types</b>				
Not reported	13% (28/223)	30% (3/10)	22% (6/27)	10% (19/186)
Supportive Care	41% (92/223)	50% (5/10)	48% (13/27)	40% (74/186)
Isotonic saline	18% (41/223)	10% (1/10)	15% (4/27)	19% (36/186)
Hypertonic (3%) saline	28% (62/223)	10% (1/10)	15% (4/27)	31% (57/186)
<b>Treatment complications</b>				
None	90% (200/223)	100% (10/10)	96% 26/27)	88% (164/186)
Rhabdomyolysis	7% (16/223)	0% (0/10)	4% (1/27)	8% (15/186)
Osmotic demyelination	3% (7/223)	0% (0/10)	0% (0/27)	4% (7/186)
<b>Outcomes</b>				
Not reported	9% (19/223)	40% (4/10)	18.5% (5/27)	5% (10/186)
Recovered (partial/complete)	78% (175/223)	60% (6/10)	77.8% (21/27)	80% (148/186)
Death	13% (29/223)	0% (0/10)	3.7% (1/27)	15% (28/186)



**Figure 4** 3D scatterplot box to group cases according to serum sodium, treatment type and severity of clinical presentation. Dots are coloured according to treatment type (hypertonic saline, red; isotonic saline, orange; other, pink or not reported, blue). 3D, three dimensions.

In the remainder, the majority recovered (78%) and 13% died (table 5 and figure 5). In addition, 11% of patients remained biochemically hyponatraemic or had recurrent episodes despite treatment. The cause of death was either unknown (10%), related to hyponatraemia and

its associated complications (eg, cerebral and pulmonary oedema or OMD syndrome) (49%) or due to other underlying conditions (cancer, pneumonia, cardiac arrest or suicide) (41%). Autopsies were conducted in 43% of patients who died and common signs of water intoxication included an enlarged stomach, duodenum and small intestine; pulmonary/cerebral oedema; a large volume of dilute cadaveric blood and a distended bladder.



**Figure 5** Categorisation of cases according to underlying comorbidities, water intake (litres per day) and outcomes.

## DISCUSSION

The aim of this systematic review was to define the clinical characteristics, treatment patterns and outcomes of excess water intake. The main findings were that: (1) the majority of studies reported that patients had a chronic psychiatric morbidity, primarily schizophrenia spectrum disorders; (2) a significant proportion of cases (41%) described patients receiving concomitant medications that are associated with hyponatraemia suggesting that multiple factors were involved in the pathogenesis of water intoxication; (3) the reasons for excessive consumption was primary due to psychogenic polydipsia but exercise and iatrogenic factors were involved in some cases; (4) the median water intake that was self-reported or observed by others was 8.0 L/day and the mean serum sodium was 118 mmol/L; (5) 28% of patients received hypertonic saline, and treatment-related complications



and death were reported in 10% and 13% of the cases/case series, respectively.

Water is essential for life and constitutes between 45% and 75% of total body weight.<sup>205</sup> National dietary guidelines recommend the consumption of 'plenty of water',<sup>206</sup> and adequate intake (AI) is defined as 2.1 L/day for adult women and 2.6 L/day for adult men based on the median water intake in the general population.<sup>206</sup> As water requirements vary widely according to multiple factors (age, gender, comorbidities, activity level, ambient temperate, basal metabolic rate) guidelines do not attempt to define a precise amount that applies to every individual or situation,<sup>205 206</sup> but rather provide broad guidance on the prevention of complications associated with acute dehydration, and no safe upper limit has been provided.<sup>27 205</sup> Furthermore, in the general population the majority (82%) do not even reach the recommended targets for water consumption<sup>207</sup> and/or self-regulate their intake, perhaps explaining why water intoxication is a rare event.

In a seminal paper published in 1923, Rowntree was the first to coin the term water intoxication and describe the salient clinical features and pathology of the syndrome in experimental animals as well as recommend hypertonic saline as a treatment.<sup>1</sup> In humans, one of the fundamental physiological flaws that contributes to water intoxication is that intestinal water absorption exceeds the maximal capacity of the kidney to excrete the load (determined to be between 735 and 970 mls per hour).<sup>6</sup> While chronic overhydration for more than 3 days leads to adaptive increases in urinary free water excretion (by increasing aquaporin-2 water channel expression in the renal collecting duct<sup>208 209</sup>) it also elevates renal solute loss<sup>130</sup> thereby lowering the threshold for water intoxication. Nevertheless, these homeostatic mechanisms are overcome by neurobehavioural factors that drive the urge to drink water.<sup>28</sup> In this regard, it is noteworthy that in mice, isolation and/or anxiety results in habitual polydipsia that reduces dopaminergic neuron excitability of the ventral tegmental area (reward area of the brain) and mediates anxiolytic and/or reward-seeking behaviour.<sup>28</sup>

In the current study, most cases (52%) suffered from schizophrenia spectrum disorders. Consistent with this finding, in a previous study, 10% of hospitalised psychiatric inpatients exhibited polydipsia and one-third were at risk of water intoxication.<sup>210</sup> Remarkably water intoxication was reported as the cause of death in 18.5% of schizophrenia inpatients under the age of 53 years old.<sup>58</sup> In our study, compulsive water intake in this population was driven by psychogenic polydipsia probably due to multiple factors including delusional beliefs and anxiety related to an acute psychotic episode; resetting of hypothalamic thirst centres; inappropriate antidiuretic hormone release; urinary solute loss due to chronic overhydration and/or concurrent concomitant medications that predispose to hyponatraemia.<sup>14 28 50 130 135 160</sup> In addition, other psychiatric disorders linked to water intoxication in our review included chronic anxiety disorder,

acute depression and potomania.<sup>62 169 174</sup> Occasionally, some cases of psychogenic polydipsia in this review were not obviously linked to a chronic psychiatric condition.<sup>139</sup> One example was a 64-year-old woman with mitral valve disease who suddenly began compulsively drinking 30–40 glasses of water for no apparent reason, leading to cerebral oedema and death.<sup>129</sup> In this case, it was suspected that the inappropriate behaviour reflected an undiagnosed psychosis<sup>139</sup> and/or an anxiety disorder.<sup>129</sup>

In this systematic review, we found that exercise was a common predisposing factor for water intoxication, especially in those without a medical or psychiatric condition.<sup>6 10 32 56 88 92 118 120 133 162 170 186 202 203</sup> In support of this finding, a case-control study of 88 participants in the London Marathon found that 12.5% (11/88) developed asymptomatic hyponatraemia (128–134 mmol/L) and that this was related in part to higher fluid intake (3683 mL vs 1924 mL).<sup>162</sup> In addition, in the Hawaiian and New Zealand triathlons biochemical and clinical hyponatraemia was detected in 27% and 18% of participants, respectively.<sup>211 212</sup> Three key factors mediate the pathogenesis of exercise-induced water intoxication<sup>213</sup>: (1) excessive sodium loss due to prolonged sweating and exercise, as in ultramarathon runners participating in distance running events; (2) aggressive intake of fluid containing low levels of electrolyte solution; and (3) individual variations in thirst perception and levels of habitual water consumption.<sup>214</sup>

Of importance, the present systematic review identified several cases of iatrogenic causes of water intoxication. The cases included medical advice provided to patients by healthcare workers to increase water intake: to prepare for an ultrasound,<sup>51 55 64 69 117 159 172 190</sup> colonoscopy<sup>136 142 190 198</sup> or prior to uroflowmetry<sup>140</sup>; prevent haemorrhagic cystitis<sup>151</sup>; during the perioperative period<sup>108 131</sup>; during labour<sup>126 204</sup>; following accidental poisoning<sup>49</sup>; during participation in a research study<sup>88</sup>; to treat a suspected urinary tract infection<sup>45</sup> and/or for potential health benefits.<sup>86 180</sup> In some of these situations, other additional exacerbating factors were identified, such as low dietary solute,<sup>198</sup> anxiety,<sup>131</sup> renal impairment,<sup>45</sup> use of complementary medicines (such as giant leaf frog venom<sup>191</sup>); recent introduction of concomitant medications that lower serum sodium (particularly thiazide diuretics or recent use of cyclophosphamide)<sup>134 151 183</sup> or the presence of a urethral stricture.<sup>45</sup> However, the key factor leading to water intoxication was misinterpretation of the medical advice provided (such as: 'drink plenty of water'; 'as much as you can'<sup>49 69</sup>) and the assumption that drinking more would lead to better outcomes ('the more you drink, the better the test results').<sup>55 159</sup> Although iatrogenic polydipsia is probably very rare, these cases highlight the need for healthcare workers to be more specific when providing instructions about the volume and rate of water intake (such as, 'drinking three glasses of water (750 mL) spread over a period of 2 hours')<sup>108 117 140 172</sup> and to adhere to evidence-based guidelines.<sup>180</sup>

Miscellaneous cases of water intoxication identified in this review included anorexia nervosa,<sup>112</sup> a self-remedy for chronic hiccups,<sup>62 93 123</sup> replacing fluids during acute gastroenteritis<sup>83 109</sup> or respiratory tract infection<sup>145</sup>; providing a urine sample for drug testing.<sup>10 128 132 167</sup> In the latter case, paruresis (difficulty urinating in public; present in up to 25% of the general population) may lead to emotion stress and antidiuretic hormone release and lower the threshold for water intoxication.<sup>128 167 215</sup> A notable case of water intoxication was reported in a flight attendant (who commenced on thiazide diuretic 2 weeks prior to presentation) also highlights the synergistic effects of low partial pressure of oxygen (which stimulates antidiuretic hormone release) with workplace advice to maintain in-flight hydration.<sup>183</sup> As discussed earlier, normal kidney function and urine outflow are essential for preventing water intoxication. This was demonstrated in the case of a 28-year-old man with a urethral stricture who was advised to drink '30–40 glasses of water' over 5 hours to treat a suspected urinary tract infection.<sup>45</sup>

In this systematic review, the median volume of water intake associated with intoxication was 8.0 L per day or 5.3 L over 4-hour period. Despite the limitations of this data (in that the volume of water recorded in most case reports was self-reported or observed, rather than actual measurements), it is interesting that this value is similar to the highest percentile (99th) of total water intake in the general population (with 5% of men consuming >6.4L/day).<sup>205</sup> In addition, it is also consistent with physiological calculations that an increase of ~5.1 L of total body water is required to reduce the serum sodium from 140 mmol/L to severe biochemical hyponatraemia (125 mmol/L).<sup>205</sup> However, as shown by the variability of this data between different cases and as discussed earlier, multiple factors (such as concurrent use of medications that lower serum sodium; loss of sodium through sweating during exercise; and/or reduced dietary intake solute) contribute to the volume of water required to develop intoxication.

As might be expected due to the publication bias, this review found that the majority of patients in case reports/case series (53%) presented with severe clinical features at presentation (seizures, coma). In addition, more than half (58%) the onset was chronic (>48 hours) most likely due to the fact that a high proportion of patients had an underlying chronic psychiatric disorder in this review. The spectrum of clinical features described in this review are all consistent with known features of hyponatraemia but do not provide any specific insights into symptoms associated with mild water intoxication.<sup>216</sup> In this regard, chronic mild hyponatraemia has been associated with a high incidence of falls in older patients as well as mild cognitive deficits,<sup>217 218</sup> and in future studies it would be important to elucidate the role that excess water intake may contribute to this problem in this population.<sup>205</sup>

Unfortunately, in this study, 13% of cases reports/cases series reported that patients died due to water intoxication.<sup>10 41 42 58 76 78 89 96 109 114 125 127 135 167 171 181 187 192 193 202</sup> In addition, 11% of those that recovered

from the acute episode remained biochemically hyponatraemic or had recurrent episodes despite treatment. The postmortem findings in patients who died were identical to Rowntree's description in experimental animals, describing cerebral oedema and gastric distension.<sup>1</sup> Because levels of serum electrolytes decrease after death, vitreous humour fluid was used to diagnose hyponatraemia in fatal cases due to its resistance to change post-mortem.<sup>135 171 193</sup>

Due to low quality of evidence in this review, it was not possible to make any specific conclusions on the management of water intoxication, such as when and if isotonic or hypertonic saline should be used. Consistent with clinical practice guidelines,<sup>216</sup> chronic mild hyponatraemia without severe clinical features was typically treated with water restriction alone, but this was often ineffective in psychiatric patients due to non-compliance.<sup>84 156</sup> To address this, behavioural interventions involving positive reinforcement were trialled to encourage compliance and self-efficacy.<sup>84</sup> Severe hyponatraemia was treated with a combination of water restriction, hypertonic saline or isotonic saline. Isotonic saline was used interchangeably, particularly when symptom onset was chronic (>48 hours) or unknown. Three per cent of case reports/case series reported OMD occurring as a complication of rapid correction, and all patients had either chronic or unknown onset of hyponatraemia, consistent with pathogenesis of this condition.<sup>219</sup> While not directly comparable, it is important to note, that the prevalence of OMD was lower in two retrospective cohorts of patients hospitalised for hyponatraemia (0.6%, 9/1490; and 0%, 0/56 patients),<sup>220 221</sup> indicating that the correction of serum sodium using conservative measures (such as fluid restriction, urea) is appropriate in patients with chronic polydipsia once severe life-threatening complications have been addressed with hypertonic saline.<sup>219 222</sup> In this review, rhabdomyolysis was reported as rare complication of both water intoxication as well as rapid correction of hyponatraemia.<sup>102 194</sup> It has been hypothesised that the overcorrection of sodium may lead to dysregulation of myocyte cell volume and fragility leading to rhabdomyolysis.<sup>194</sup>

There were several limitations in this systematic review. First, most of the data were derived from case reports or case series of severe clinical cases of water intoxication, and the characteristics of milder cases have not been captured. Furthermore, for this reason the true population-based prevalence of water intoxication cannot be determined from the data in this study. Second, the heterogeneity in reporting the volume of water consumed as well as the exposure time, and the inclusion of self-reported or observed volumes in the absence of standardised method reduces the precision of this estimate. Third, 'total fluid intake' was assumed to consist of plain water though this may not have been the case. Fourth, data were incomplete in up to 5%–30% of studies. Finally, other rare long-term

complications of excessive fluid intake (obstructive uropathy leading to renal impairment, cardiac failure, gastrointestinal dilatation, osteopenia with increased fracture risk) were not assessed in this systematic review.<sup>5 223</sup>

In summary, severe water intoxication is a rare syndrome but hospitalisation and healthcare utilisation as well as morbidity and mortality may be a common outcome. An underlying chronic psychiatric condition (52%) causing psychogenic polydipsia was the most frequent clinical factor involved, whereas in otherwise healthy individuals, exercise, iatrogenic, habitual/dipsogenic-associated polydipsia accounted for 33% of reported cases. Moreover, the median water consumption was much higher than population-based recommendations and consistent with physiological values suspected with the risk of harm.<sup>205 206</sup> The results of this review findings provide evidence regarding the potential dangers of overhydration and remind healthcare practitioners to be vigilant about providing clear and specific education regarding water intake to patients, especially in those that might be susceptible to misunderstanding this information.

#### Author affiliations

<sup>1</sup>Michael Stern Laboratory for Polycystic Kidney Disease, Westmead Institute for Medical Research, Westmead, New South Wales, Australia

<sup>2</sup>Department of Renal Medicine, Westmead Hospital, Westmead, New South Wales, Australia

<sup>3</sup>School of Life and Environmental Sciences, The University of Sydney, Camperdown, New South Wales, Australia

<sup>4</sup>Nutrition and Dietetics, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia

<sup>5</sup>School of Public Health, The University of Sydney, Sydney, New South Wales, Australia

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#### ORCID iDs

Alexandra Munt <http://orcid.org/0000-0002-9049-1821>

Martin Howell <http://orcid.org/0000-0001-9740-712X>

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