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**Table S1:** Study characteristics and quality scores of single TIH case reports.

| No. | Author et al. | Year | No. of TIH subjects | Study design | Country | Setting | Hyponatremia definition | Quality score | Reference |
|-----|---------------|------|---------------------|--------------|---------|---------|-------------------------|---------------|-----------|
| 1   | Achinger      | 2006 | 1                   | Case series  | USA     | Primary care | 104 mM                  | 3             | 16        |
| 2   | Adrogue       | 2000 | 1                   | Review with case report | USA | Primary care | <136 mM                  | 2             | 17        |
| 3   | Al-Salman     | 2001 | 1                   | Case report  | USA     | Secondary care | 115 mM                  | 4             | 18        |
| 4   | Ayus          | 2003 | 1                   | Case report  | USA     | Secondary care | 116 mM                  | 3             | 19        |
| 5   | Benfield      | 1986 | 1                   | Case report  | UK      | Secondary care | 124 mM                  | 3             | 20        |
| 6   | Berl          | 2010 | 1                   | Case report  | USA     | Primary care | 96 mM                   | 3             | 21        |
| 7   | Cakir         | 2010 | 1                   | Case report  | Turkey  | Secondary care | 119 mM                  | 3             | 22        |
| 8   | Coler         | 2012 | 1                   | Case Report  | USA     | Secondary care | 120 mM                  | 4             | 23        |
| 9   | Collier       | 1987 | 1                   | Case report  | UK      | Secondary care | 115 mM                  | 5             | 24        |
| 10  | Cundy         | 1981 | 1                   | Case report  | UK      | Primary care  | 99 mM                   | 4             | 25        |
| 11  | Eastell       | 1984 | 1                   | Case report  | UK      | Primary care  | 107 mM                  | 5             | 26        |
| 12  | Fadel         | 2009 | 1                   | Case report and rechallenge study | Belgium | Secondary care | 113 mM                  | 5             | 27        |
| 13  | Fuisz         | 1962 | 1                   | Case report and rechallenge study | USA | Secondary care | 121 mM                  | 4             | 28        |
| 14  | Gardner       | 2000 | 1                   | Case report  | USA     | Secondary care | 110 mM                  | 1             | 29        |
| 15  | Ghose         | 1977 | 1                   | Case report  | UK      | Primary care  | 127 mM                  | 3             | 30        |
| 16  | Gossain       | 1976 | 1                   | Case series  | USA     | Secondary care | <132 mM                  | 4             | 31        |
| 17  | Hamburger     | 1981 | 1                   | Case report  | USA     | Primary care  | 107 mM                  | 3             | 32        |
| 18  | Handler       | 2008 | 1                   | Case report  | USA     | Secondary care | <135 mM                  | 3             | 33        |
|   | Last name  | Year  | Study Type          | Country        | Setting            | Baseline Blood Sugar (mM) | Follow-up Period | Reference |
|---|------------|-------|---------------------|----------------|--------------------|---------------------------|-----------------|-----------|
| 19 | Husby     | 1981  | Case report         | Denmark        | Primary care       | 104 mM                   | 4               | 34        |
| 20 | Hussain   | 2011  | Case report         | Ireland        | Secondary care     | 99 mM                    | 2               | 35        |
| 21 | Jen       | 2002  | Case report         | China          | Secondary care     | <137 mM                  | 4               | 36        |
| 22 | Johnson   | 1983  | Case report         | USA            | Primary care       | 108 mM                   | 6               | 37        |
| 23 | Karp      | 1993  | Retrospective study | USA            | Primary care       | 104 mM                   | 1               | 38        |
| 24 | Kennedy   | 1970  | Case report         | USA            | Secondary care     | ≤108 mM                  | 4               | 39        |
| 25 | Kone      | 1986  | Case report         | USA            | Secondary care     | 118 mM                   | 4               | 40        |
| 26 | Lin       | 2002  | Case report         | China          | Secondary care     | 94 mM                    | 2               | 41        |
| 27 | Luft      | 1998  | Case report         | Germany        | Primary care       | 115 mM                   | 2               | 42        |
| 28 | Lundbom   | 1993  | Case report         | Finland        | Secondary care     | <116 mM                  | 2               | 43        |
| 29 | Mataverde | 1974  | Case report         | USA            | Secondary care     | 109 mM                   | 3               | 44        |
| 30 | Menashe   | 2000  | Case report         | Israel         | Primary care       | 106 mM                   | 3               | 45        |
| 31 | Meuleman  | 1996  | Case report         | USA            | Primary care       | 116 mM                   | 4               | 46        |
| 32 | Miyasaka  | 2013  | Case report         | Japan          | Secondary care     | (Not specified)           | 4               | 47        |
| 33 | Mok       | 2008  | Case report         | China          | Secondary care     | 111                       | 3               | 48        |
| 34 | Mouallem  | 1983  | Cohort study        | Israel         | Secondary care     | (Not specified)           | 3               | 49        |
| 35 | Mount     | 2009  | Case vignette       | USA            | Secondary care     | 113 mM                   | 4               | 50        |
| 36 | Moussa    | 1998  | Case report         | United Arab Emirates | Secondary care  | 110 mM                   | 3               | 51        |
| 37 | Mozes     | 1986  | Case report         | Israel         | Secondary care     | 104 mM                   | 4               | 52        |
| 38 | Onozaki   | 2001  | Case report         | Japan          | Primary care       | 124 mM                   | 3               | 53        |
| 39 | Orija     | 2001  | Case report         | USA            | Secondary care     | <136 mM                  | 2               | 54        |
| 40 | Ponte     | 1982  | Case report         | USA            | Secondary care     | 115 mM                   | 2               | 55        |
| No. | Author et al. | Year | No. of TIH subjects | Study design | Country | Setting | Hyponatremia definition | Quality score | Reference |
|-----|--------------|------|---------------------|--------------|---------|---------|-------------------------|-------------|-----------|
| 1   | Aaseth       | 2001 | 3                   | Case series  | Norway  | Primary care | <125 mM                 | 4           | 65        |
| 2   | Adams        | 1988 | 2                   | Clinical survey | UK     | Secondary care | <130 mM                | 4           | 66        |
| 3   | Al Qahtani   | 2013 | 469                 | Case series  | Saudi Arabia | Secondary care | ≤135 mM               | 4           | 67        |
| 4   | Ambrosi.     | 2004 | 3                   | Case reports  | France  | Secondary care | ≤116 mM                | 3           | 68        |
| 5   | Ashraf       | 1981 | 7                   | Case reports  | USA     | Primary care | ≤116 mM                | 4           | 69        |
| 6   | Bain         | 1986 | 2                   | Case report   | UK      | Secondary care | 112 mM                | 3           | 70        |
| 7   | Bayer AJ     | 1986 | 21                  | Case series   | UK      | Secondary care | <130 mM               | 5           | 71        |

**Table S2:** Characteristics and quality scores of studies included in the meta-analysis i.e. where more than one TIH patient was reported per study.
|   | Author       | Year | Method                                                                 | Country | Setting                | Title                                                                 | Blood glucose threshold | Total | N  |
|---|--------------|------|------------------------------------------------------------------------|---------|------------------------|----------------------------------------------------------------------|--------------------------|-------|----|
|8  | Bissram      | 2007 | Retrospective cohort study                                            | USA     | Secondary care         | <134 mM                                                               | 7                        | 72    |
|9  | Booker       | 1984 | Case reports                                                          | Australia | Secondary care         | <121 mM                                                               | 6                        | 73    |
|10 | Canning G    | 1988 | Case reports                                                          | UK      | (Not specified)        | ≤125 mM                                                               | 4                        | 74    |
|11 | Chapman MD   | 2002 | Descriptive analysis using case reports                               | Australia | (Not specified)        | (Not specified)                                                       | 3                        | 75    |
|12 | Chow         | 2004 | Case series                                                           | China   | Secondary care         | <130 mM                                                               | 6                        | 76    |
|13 | Clayton       | 2006 | Cross sectional observational study                                    | UK      | Primary care           | <135 mM                                                               | 4                        | 77    |
|14 | Coenraad     | 2003 | Case series                                                           | The Netherlands | Secondary care         | ≤130 mM                                                               | 5                        | 78    |
|15 | Cogan        | 1983 | Case series                                                           | Belgium | Secondary care         | <135 mM                                                               | 3                        | 79    |
|16 | Donaldson    | 1983 | Case-controlled clinical trial                                        | Australia | Secondary care         | <134 mM                                                               | 3                        | 80    |
|17 | Fenske       | 2009 | Prospective observational study                                       | Germany | Secondary care         | <130 mM                                                               | 5                        | 81    |
|18 | Fichman      | 1971 | Case series and rechallenge study                                      | USA     | Secondary care         | ≤118 mM                                                               | 6                        | 82    |
|19 | Fourlanos     | 2003 | Case reports                                                          | Australia | (Not specified)        | (Not specified)                                                       | 1                        | 83    |
|20 | Frenkel      | 2010 | Controlled clinical trial                                             | The Netherlands | (Not specified)        | (Not specified)                                                       | 4                        | 84    |
|21 | Friedman     | 1989 | Prospective controlled study                                          | Israel  | Secondary care         | <130 mM                                                               | 7                        | 85    |
|22 | Ghose        | 1975 | Case reports                                                          | UK      | Secondary care         | (Not specified)                                                       | 2                        | 86    |
|23 | Hajjar       | 2004 | Case reports                                                          | USA     | Secondary care         | ≤130 mM                                                               | 3                        | 87    |
|24 | Hoorn        | 2006 | Prospective cohort study                                              | The Netherlands | Secondary care         | ≤125 mM                                                               | 7                        | 88    |
|25 | Hung         | 2002 | Case series                                                           | China   | Secondary care         | ≤113 mM                                                               | 4                        | 89    |
|26 | Hwang        | 2010 | Case series                                                           | Korea   | Secondary care         | ≤128 mM                                                               | 2                        | 90    |
|27 | Johnston     | 1989 | Case series                                                           | UK      | Secondary care         | ≤130 mM                                                               | 3                        | 91    |
|28 | Jolobe       | 2003 | Case series (letter)                                                  | UK      | (Not specified)        | <120 mM                                                               | 2                        | 92    |
|29 | Kalksma      | 2002 | Case reports                                                          | The Netherlands | Primary care           | <120 mM                                                               | 3                        | 93    |
|30 | Kinoshita    | 2011 | Case series                                                           | Japan   | National registry      | (Not specified)                                                       | 3                        | 94    |
|   | First name | Year | Case Type | Location | Setting | Reference | Statistic | n | ID |
|---|------------|------|-----------|----------|---------|-----------|-----------|---|----|
| 31 | Mackay    | 1983 | Case series | New Zealand | Secondary care | ≤132 mM | 3 | 95 |
| 32 | Malin     | 1997 | Case series | USA | Secondary care | <130 mM | 6 | 96 |
| 33 | Mathew    | 1990 | Case reports | Australia | Secondary care | ≤130 mM | 4 | 97 |
| 34 | McDowell  | 2010 | Retrospective cohort study | UK | Primary care | ≤130 mM | 6 | 98 |
| 35 | Moualem   | 1991 | Case reports | Israel | Secondary care | 117 mM | 4 | 99 |
| 36 | Musch     | 2001 | Consecutive case series | Belgium | Secondary care | ≤130 mM | 5 | 100 |
| 37 | Oles      | 1984 | Case reports | USA | Primary care | ≤129 mM | 2 | 101 |
| 38 | Pinnock   | 1978 | Case series | Channel Islands | Secondary care | ≤128 mM | 2 | 102 |
| 39 | Rask      | 1996 | Case reports | Sweden | Primary care | ≤121 mM | 3 | 103 |
| 40 | Rastogi   | 2012 | Retrospective, case-controlled study | USA | Secondary care | <135 mM | 8 | 104 |
| 41 | Rodenburg | 2013 | Population-based cohort study | Netherlands | Primary care | ≤135 mM | 4 | 105 |
| 42 | Rosner    | 2004 | Case reports | USA | Secondary care | ≤122 mM | 4 | 106 |
| 43 | Shapiro   | 2010 | Prospective, observational, non-interventional study | Israel | Secondary care | ≤125 mM | 6 | 107 |
| 44 | Sharabi   | 2002 | Case series | USA | Secondary care | <135 mM | 5 | 108 |
| 45 | Sonnenblick | 1986 | Case series | Israel | Clinical trial | <120 mM | 4 | 109 |
| 46 | Sonnenblick | 1989 | Case reports | Israel | Secondary care | <115 mM | 3 | 110 |
| 47 | Takeshita | 2010 | Case reports | Japan | Secondary care | ≤118 mM | 1 | 111 |
| 48 | Tarssanen | 1980 | Case reports | Finland | Secondary care | 111 mM | 5 | 112 |
| 49 | Thuesen   | 1980 | Case reports | Denmark | Primary care | 113 mM | 2 | 113 |
| 50 | van Brummelen | 1978 | Case-controlled clinical trial | The Netherlands | Secondary care | (Not specified) | 7 | 114 |
| 51 | Van Wijngaarden | 2010 | Case reports | The Netherlands | Primary care | <135 mM | 2 | 115 |
| 52 | Yong      | 2011 | Case series | Australia | Secondary care | <135 mM | 5 | 116 |
|   | Zalin | 1984 | 8 | Case reports | UK | Secondary care | ≤129 mM | 4 | 117 |
### Table S3: Meta-analyses of demographic characteristics of patients with Thiazide-Induced Hyponatremia by analysis of quality score, year of publication and age of patient.

| Symptoms         | Quality Score high |           | Quality Score Low |           | Year of publication Later |           | Year of publication earlier |           | Age of population younger |           | Age of population older |           |
|------------------|-------------------|-----------|-------------------|-----------|--------------------------|-----------|-----------------------------|-----------|---------------------------|-----------|-------------------------|-----------|
|                  | Mean   | 95% CI  | I² (%) | Mean   | 95% CI  | I² (%) | Mean   | 95% CI  | I² (%) | Mean   | 95% CI  | I² (%) |
| Gender (Female)* | 0.77   | 0.72 to 0.81 | 70     | 0.84   | 0.76 to 0.91 | 38     | 0.79   | 0.75 to 0.84 | 76     | 0.77   | 0.61 to 0.84 | 36     | 0.73   | 0.69 to 0.76 | 15     | 0.84   | 0.76 to 0.90 | 66     |
| Age (years)      | 73.4   | 71.3 to 75.5 | 92     | 76.9   | 72.8 to 81.0 | 92     | 78.1   | 75.5 to 80.7 | 96     | 71.3   | 68.2 to 74.5 | 81     | 69.2   | 67.3 to 71.1 | 74     | 79.7   | 77.6 to 81.9 | 87     |
| Time to TH (days)| 23.5   | 3.1 to 44.0 | 96     | 12.0   | 2.6 to 21.4 | 79     | 81.3   | 20.5 to 142.1 | 81     | 6.9    | 9.5 to 62.8 | 47     | 27.2   | 8.1 to 46.3 | 98     | 9.5    | -4.9 to 23.8 | 77     |

Prevalence estimates from meta-analysis and confidence intervals are all expressed as proportions.
Table S4: Meta-analyses of clinical characteristics of patients with Thiazide-Induced Hyponatremia by analysis of quality score, year of publication and age of patient. Prevalence estimates from meta-analysis and confidence intervals are all expressed as proportions.

| Symptoms      | Quality Score high | Quality Score Low | Year of publication Later | Year of publication earlier | Age of population younger | Age of population older |
|---------------|--------------------|-------------------|---------------------------|-----------------------------|--------------------------|------------------------|
|               | Prop               | 95% CI            | Prop                      | 95% CI                      | Prop                     | 95% CI                 | Prop                     | 95% CI | Prop                     | 95% CI | Prop                     | 95% CI |
|               | ⍺ (%)              |                   |                           |                             | ⍺ (%)                    |                       | ⍺ (%)                   |                   | ⍺ (%)                   |           | ⍺ (%)                   |           |
| Fatigue       | 0.54               | 0.32 to 0.75      | 66                        | 0.19                        | 0.002 to 0.65            | *                      | 0.36                    | 0.39 to 0.41 | 96                  | 0.50 | 0.15 to 0.85             | 74          | 0.58 | 0.24 to 0.89             | 73          | 0.49 | 0.42 to 0.55             | *          |
| Dizziness     | 0.31               | 0.14 to 0.51      | 93                        | 1 study                     | -                        | -                      | 0.39                    | 0.11 to 0.72 | 97                  | 0.18 | 0.11 to 1.00             | *          | 0.72 | 0.18 to 1.00             | 96          | 0.17 | 0.13 to 0.23             | 66          |
| Confusion     | 0.40               | 0.27 to 0.54      | 85                        | 0.56                        | 0.29 to 0.81             | 77                      | 0.35                    | 0.20 to 0.51 | 90                  | 0.54 | 0.37 to 0.70             | 67          | 0.39 | 0.26 to 0.54             | 38          | 0.35 | 0.20 to 0.51             | 90          |
| Vomiting      | 0.37               | 0.29 to 0.45      | 40                        | 0.30                        | 0.06 to 0.63             | 63                      | 0.34                    | 0.22 to 0.46 | 81                  | 0.37 | 0.20 to 0.56             | 44          | 0.37 | 0.20 to 0.56             | 44          | 0.37 | 0.31 to 0.44             | 26          |
| Falls         | 0.46               | 0.16 to 0.77      | 90                        | 1 study                     | -                        | -                      | 0.30                    | 0.10 to 0.56 | 68                  | 0.72 | 0.18 to 1.00             | *          | 0.72 | 0.18 to 1.00             | *          | 0.31 | 0.10 to 0.58             | 66          |
| Nausea        | 0.35               | 0.21 to 0.49      | 78                        | 0.23                        | 0.15 to 0.32             | 77                      | 0.25                    | 0.19 to 0.32 | 17                  | 0.44 | 0.21 to 0.68             | 84          | 0.41 | 0.17 to 0.68             | 82          | 0.28 | 0.22 to 0.34             | 0           |
| Unconsciousness | 0.26             | 0.06 to 0.53      | 78                        | 0.40                        | 0.10 to 0.74             | 77                      | 0.40                    | 0.04 to 0.85 | 83                  | 0.29 | 0.10 to 0.52             | 73          | 0.35 | 0.10 to 0.65             | 82          | 0.43 | 0.19 to 0.68             | 0           |
| Weakness      | 0.37               | 0.24 to 0.51      | 45                        | 0.62                        | 0.38 to 0.84             | 40                      | 0.51                    | 0.28 to 0.73 | 59                  | 0.42 | 0.24 to 0.61             | 45          | 0.45 | 0.28 to 0.63             | 44          | -   | -                        | 0           |
| Neurological Symptoms | 0.46 | 0.09 to 0.85      | 85                        | 0.60                        | 0.25 to 0.90             | 25                      | 0.97                    | 0.82 to 0.99 | *                      | 0.29 | 0.15 to 0.46             | 0           | 0.25 | 0.10 to 0.44             | 0           | 0.76 | 0.37 to 0.99             | 68          |
| Seizures      | 0.16               | 0.05 to 0.32      | 81                        | 0.40                        | 0 to 0.97                | 91                      | 0.06                    | 0.01 to 0.15 | 74                  | 0.32 | 0.13 to 0.56             | 70          | 0.34 | 0.13 to 0.58             | 71          | 0.12 | 0.0 to 0.42              | 81          |
| Diabetes      | 0.26               | 0.09 to 0.47      | 99                        | 0.43                        | 0.11 to 0.78             | *                      | 0.30                    | 0.12 to 0.52 | 99                  | 0.18 | 0.03 to 0.41             | *          | 0.18 | 0.03 to 0.41             | 96          | 0.22 | 0.19 to 0.27             | 0           |
| CVD           | 0.30               | 0.20 to 0.41      | 42                        | 0.79                        | 0.56 to 0.95             | 25                      | 0.39                    | 0.21 to 0.60 | 79                  | 0.56 | 0.31 to 0.79             | 61          | 0.51 | 0.22 to 0.80             | 66          | 0.47 | 0.28 to 0.67             | 77          |

CardioVascular Disease (CVD), Prop (proportion), Confidence Interval (CI). None of these factors explain the high levels of heterogeneity between these studies. Prevalence estimates from meta-analysis and Confidence intervals are all expressed as proportions, * denotes less than 3 studies and therefore not possible to assess heterogeneity.
Table S5: Meta-analyses of drug history of patients with Thiazide-Induced Hyponatremia by analysis of quality score, year of publication and age of patient. Prevalence estimates from meta-analysis and confidence intervals are all expressed as proportions.

| Symptoms                  | Quality Score high | Quality Score Low | Year of publication Later | Year of publication earlier | Age of population younger | Age of population older |
|---------------------------|--------------------|-------------------|---------------------------|-----------------------------|---------------------------|-------------------------|
|                           | Proportion  | 95% CI | I² (%) | Proportion  | 95% CI | I² (%) | Proportion  | 95% CI | I² (%) | Proportion  | 95% CI | I² (%) | Proportion  | 95% CI | I² (%) |
| Thiazide                  |                |        |        |            |        |        |            |        |        |            |        |        |            |        |        |
| HCTZ                      | 0.76          | 0.63 to 0.87 | 93    | 0.59       | 0.14 to 0.96 | 97    | 0.67       | 0.46 to 0.85 | 98    | 0.69       | 0.50 to 0.86 | 43    | 0.63       | 0.61 to 0.65 | 0     | 0.73       | 0.45 to 0.94 | 78    |
| Indapamide                | 0.53          | 0.13 to 0.91 | 99    | 0.54       | 0.49 to 0.58 | 93    | 0.47       | 0.23 to 0.72 | 99    | -            | - | - | 1 study | - | - | 0.83 | 0.51 to 0.99 | 62    |
| Moduretic®               | 0.80          | 0.57 to 0.96 | 85    | 0.42       | 0.37 to 0.46 | 72    | 0.39       | 0.34 to 0.42 | 90    | 0.84       | 0.69 to 0.95 | 74    | 0.92       | 0.78 to 0.99 | 64    | 0.64       | 0.37 to 0.88 | 40    |
| Bendroflumethiazide       | 0.56          | 0.11 to 0.95 | 97    | 0.37       | 0.21 to 0.54 | * | 0.83       | 0.34 to 0.59 | 97    | 0.27       | 0.10 to 0.50 | 63    | 0.61       | 0.10 to 0.99 | 97    | 1 study | - | * |
| Chlortalidone             | 0.04          | 0.01 to 0.09 | 87    | 0.43       | 0.11 to 0.78 | * | 0.02       | 0.002 to 0.05 | 73    | 0.24       | 0.11 to 0.40 | * | 0.04       | 0.009 to 0.09 | 87    | 0.43       | 0.11 to 0.79 | * |
| Other Drugs               |                |        |        |            |        |        |            |        |        |            |        |        |            |        |        |
| ACE inhibitor             | 0.35          | 0.12 to 0.67 | 98    | 0.83       | 0.44 to 1.00 | * | 0.42       | 0.17 to 0.68 | 97    | 1 study | - | * | 0.76 | 0.34 to 0.99 | * | 0.28 | 0.16 to 0.41 | 25    |
| NSAID                     | 0.32          | 0.30 to 0.34 | 93    | 0.37       | 0.09 to 0.71 | * | 0.32       | 0.15 to 0.51 | 93    | 0.37       | 0.09 to 0.71 | * | 0.48 | 0.18 to 0.79 | 60    | 0.16 | 0.12 to 0.21 | 0    |
| Non-thiazide diuretics    | 0.20          | 0.18 to 0.22 | * | 0.80       | 0.39 to 1.00 | 60    | 0.44       | 0.13 to 0.80 | 76    | 1 study | - | * | 0.59 | 0.003 to 0.98 | * | 0.57 | 0.19 to 0.93 | 56    |
| Antidepressants           | 0.29          | 0.16 to 0.44 | 75    | 0.50       | 0.18 to 0.82 | * | 0.38       | 0.16 to 0.63 | 64    | -            | - | - | 0.53 | 0.002 to 1.00 | * | 0.33 | 0.23 to 0.43 | 0    |

HydroChloroThiaZide (HCTZ), AngioTensin Converting enzyme (ACE) inhibitor, Non-Steroidal AntiInflammatory Drug (NSAID), Prop (proportion), Confidence Interval (CI). None of these factors explain the high levels of heterogeneity between these studies. Prevalence estimates from meta-analysis and Confidence intervals are all expressed as proportions, * denotes less than 3 studies and therefore not possible to assess heterogeneity.
Table S6: Meta-analyses of laboratory characteristics of patients with Thiazide-Induced Hyponatremia by analysis of quality score, year of publication and age of patient.

| Symptoms                        | Quality Score high | Quality Score Low | Year of publication Later | Year of publication earlier | Age of population younger | Age of population older |
|---------------------------------|--------------------|-------------------|---------------------------|----------------------------|---------------------------|-------------------------|
|                                 | Mean | 95% CI | I² (%) | Mean | 95% CI | I² (%) | Mean | 95% CI | I² (%) | Mean | 95% CI | I² (%) | Mean | 95% CI | I² (%) |
| Serum sodium (mM)               | 116.2 | 112.2 to 120.3 | 99 | 116.8 | 112.8 to 120.7 | 96 | 117.1 | 113.1 to 121.1 | 98 | 115.9 | 112.3 to 119.5 | 98 | 116.0 | 110.5 to 121.6 | 99 | 115.6 | 112.4 to 118.8 | 96 |
| Serum potassium (mM)            | 3.4 | 3.1 to 3.7 | 96 | 3.0 | 2.8 to 3.2 | 72 | 3.3 | 3.0 to 3.7 | 98 | 3.2 | 3.0 to 3.4 | 88 | 3.2 | 2.8 to 3.7 | 96 | 3.3 | 3.0 to 3.6 | 95 |
| Serum creatinine (µmol/L)       | 79.5 | 57.4 to 91.0 | 95 | 79.9 | 64.7 to 91.0 | 97 | 71.7 | 53.9 to 89.5 | 95 | 80.7 | 62.1 to 99.4 | 99 | 80.7 | 55.5 to 102.9 | 99 | 72.0 | 60.5 to 83.5 | 96 |
| Serum osmolality mosm/kg        | 239.2 | 234.1 to 244.4 | 85 | 242.0 | 237.8 to 246.1 | 51 | 236.3 | 231.7 to 240.9 | 70 | 244.2 | 237.3 to 251.0 | 75 | 241.9 | 230.8 to 253.1 | 75 | 239.3 | 234.7 to 243.9 | 81 |
| Urine osmolality mosm/kg        | 392.4 | 364.7 to 420.1 | 69 | 415.9 | 377.6 to 500.2 | 74 | 399.2 | 362.6 to 435.8 | 87 | 402.8 | 329.3 to 476.3 | 89 | 420.8 | 365.6 to 476.1 | 88 | 377.9 | 341.7 to 414.1 | 51 |
| Urine sodium (mM)               | 66.1 | 39.8 to 92.4 | 94 | 62.2 | 44.6 to 79.5 | 67 | 79.4 | 68.2 to 90.6 | 96 | 49.0 | 28.5 to 69.6 | 0 | 53.6 | 34.0 to 73.1 | 95 | 79.3 | 47.0 to 81.0 | 22 |

Prevalence estimates from meta-analysis and confidence intervals are all expressed as proportions. None of these factors explain the high levels of heterogeneity between these studies. Prevalence estimates from meta-analysis and Confidence intervals are all expressed as proportions.
Meta-analyses graphs

Clinical characteristics and symptoms

Figure S1 Proportion of patients with thiazide-induced hyponatremia who were female.
Proportion meta-analysis plot [random effects]

| Study            | Proportion | 95% Confidence Interval |
|------------------|------------|-------------------------|
| Asteth 2001      | 1.000      | (0.292, 1.000)          |
| Ambrosi 2004     | 1.000      | (0.292, 1.000)          |
| Ashraf 1981      | 0.714      | (0.290, 0.963)          |
| Bain 1986        | 1.000      | (0.158, 1.000)          |
| Bauer 1986       | 0.591      | (0.364, 0.793)          |
| Booker 1984      | 1.000      | (0.541, 1.000)          |
| Canning 1988     | 1.000      | (0.398, 1.000)          |
| Chapman 2002     | 0.826      | (0.755, 0.883)          |
| Chow 2004        | 0.700      | (0.635, 0.759)          |
| Clayton 2006     | 0.667      | (0.299, 0.925)          |
| Conrard 2003     | 0.667      | (0.094, 0.992)          |
| Cogan 1983       | 1.000      | (0.398, 1.000)          |
| Ferske 2009      | 0.889      | (0.518, 0.997)          |
| Fichman 1971     | 0.800      | (0.593, 0.932)          |
| Frenk 2010       | 0.615      | (0.316, 0.861)          |
| Friedman 1989    | 0.727      | (0.390, 0.940)          |
| Hajar 2004       | 1.000      | (0.158, 1.000)          |
| Hung 2002        | 0.429      | (0.099, 0.816)          |
| Hwang 2010       | 1.000      | (0.768, 1.000)          |
| Johnston 1989    | 1.000      | (0.292, 1.000)          |
| Jolobe 2003      | 0.846      | (0.651, 0.955)          |
| Kalkama 2002     | 0.667      | (0.094, 0.992)          |
| Kinoshita 2011   | 0.625      | (0.458, 0.773)          |
| Malin 1997       | 0.750      | (0.349, 0.968)          |
| Mathew 1990      | 0.759      | (0.628, 0.881)          |
| McDowell 2010    | 0.738      | (0.688, 0.784)          |
| Moulten 1983     | 0.250      | (0.006, 0.806)          |
| Musch 2001       | 0.632      | (0.384, 0.837)          |
| Nies 1984        | 1.000      | (0.292, 1.000)          |
| Pinnock 1978     | 1.000      | (0.398, 1.000)          |
| Rask 1996        | 1.000      | (0.292, 1.000)          |
| Rastogi 2012     | 0.708      | (0.686, 0.728)          |
| Rodenburg 2013   | 0.868      | (0.807, 0.916)          |
| Rosner 2004      | 1.000      | (0.158, 1.000)          |
| Shapiro 2010     | 0.923      | (0.830, 0.975)          |
| Sharabi 2002     | 0.828      | (0.765, 0.880)          |
| Takeshita 2010   | 1.000      | (0.158, 1.000)          |
| Tarssanen 1980   | 1.000      | (0.292, 1.000)          |
| Thuesen 1980     | 1.000      | (0.158, 1.000)          |
| Van Wijngaarden 2010 | 1.000      | (0.158, 1.000) |
| Yong 2011        | 1.000      | (0.715, 1.000)          |
| Zalin 1984       | 0.625      | (0.245, 0.915)          |
| van Brummelen 1978 | 0.000    | (0.000, 0.842)          |

Combined: 0.785 (0.744, 0.823)
Figure S2. Summary of mean age in patients with thiazide-induced hyponatremia.

| Authorship | Year of publication | ES (95% CI) | % Weight |
|------------|---------------------|-------------|----------|
| Aaseth     | 2001                | 75.00 (62.55, 87.45) | 1.49     |
| Ambrosi    | 2004                | 84.33 (80.36, 88.30) | 3.47     |
| Astraf     | 1981                | 68.29 (60.75, 75.83) | 2.49     |
| Booker     | 1984                | 67.00 (61.72, 72.28) | 3.11     |
| Canning    | 1988                | 75.00 (66.57, 83.43) | 2.27     |
| Chow       | 2004                | 76.00 (74.82, 77.19) | 4.02     |
| Clayton    | 2006                | 64.20 (55.03, 73.37) | 2.10     |
| Coenraad   | 2003                | 80.67 (75.22, 96.12) | 1.11     |
| Cogan      | 1983                | 76.50 (74.34, 78.66) | 3.88     |
| Fenske     | 2009                | 76.00 (68.16, 83.84) | 2.42     |
| Fichman    | 1971                | 60.96 (57.13, 64.79) | 3.50     |
| Friedman   | 1989                | 71.00 (65.50, 76.40) | 3.08     |
| Hajar      | 2004                | 80.50 (78.56, 83.44) | 3.72     |
| Hung       | 2002                | 76.71 (69.69, 83.73) | 2.63     |
| Hwang      | 2010                | 76.00 (72.86, 79.14) | 3.67     |
| Johnston   | 1989                | 65.67 (62.40, 68.94) | 3.64     |
| Kalksma    | 2002                | 86.00 (79.21, 92.79) | 2.69     |
| Kinoshita  | 2011                | 76.40 (73.83, 78.97) | 3.80     |
| Mackay     | 1983                | 69.09 (63.54, 74.64) | 3.03     |
| McDowell   | 2010                | 73.10 (71.97, 74.23) | 4.02     |
| Mouallem   | 1983                | 66.75 (52.21, 81.29) | 1.21     |
| Musch      | 2001                | 75.00 (70.50, 79.50) | 3.33     |
| Oles       | 1984                | 81.33 (70.82, 91.84) | 1.82     |
| Pinnock    | 1978                | 77.50 (70.57, 84.43) | 2.65     |
| Rask       | 1996                | 79.33 (72.14, 86.52) | 2.58     |
| Rastogi    | 2012                | 71.10 (70.53, 71.67) | 4.07     |
| Rosner     | 2004                | 73.50 (52.93, 94.07) | 0.71     |
| Shapiro    | 2010                | 82.10 (79.99, 84.21) | 3.89     |
| Sharabi    | 2002                | 76.40 (75.00, 77.80) | 3.99     |
| Sonnenblick| 1986                | 77.30 (70.56, 84.04) | 2.70     |
| Takeshita  | 2010                | 71.00 (57.28, 84.72) | 1.31     |
| Tarssanen  | 1980                | 74.00 (62.24, 85.76) | 1.80     |
| Thuesen    | 1980                | 61.00 (49.25, 72.75) | 1.60     |
| Van Wijngaarden | 2010 | 82.50 (73.69, 91.31) | 2.18     |
| Yong       | 2011                | 81.70 (78.27, 85.13) | 3.81     |
| Zalin      | 1984                | 65.12 (57.98, 72.26) | 2.60     |
| Overall    | (I-squared = 92.6%, p = 0.000) | 74.94 (73.03, 76.85) | 100.00   |

NOTE: Weights are from random effects analysis

![Age Distribution Chart]
**Figure S3.** Summary of mean Body Mass Index in patients with thiazide-induced hyponatremia (Kg/m²).

| Authorship | Year of publication | ES (95% CI) | Weight |
|------------|---------------------|------------|--------|
| Chow       | 2004                | 22.40 (21.91, 22.89) | 49.92  |
| Rastogi    | 2012                | 27.40 (27.10, 27.70) | 50.08  |
| Overall    | (I² = 99.7%, p = 0.000) | 24.90 (20.00, 29.80) | 100.00 |

NOTE: Weights are from random effects analysis.
Figure S4. Summary of mean duration from thiazide initiation to presentation with thiazide-induced hyponatremia (days).

| Authorship | Year of publication | ES (95% CI) | Weight |
|------------|---------------------|-------------|--------|
| Ashraf     | 1981                | 5.67 (1.82, 9.52) | 10.88  |
| Bain       | 1986                | 4.00 (2.05, 5.95)  | 10.99  |
| Booker     | 1984                | 7.60 (3.20, 12.00) | 10.84  |
| Clayton    | 2006                | 470.00 (145.30, 794.70) | 0.11  |
| Fichman    | 1971                | 17.43 (2.06, 32.80) | 9.09   |
| Friedman   | 1989                | 6.67 (3.46, 9.88)  | 10.92  |
| Hung       | 2002                | 737.00 (–891.26, 2165.26) | 0.01  |
| Kalksma    | 2002                | 1095.00 (511.10, 1678.90) | 0.04  |
| McDowell   | 2010                | 64.88 (59.33, 70.43)  | 10.73  |
| Mouallem   | 1983                | 172.00 (–48.50, 392.50) | 0.25  |
| Oles       | 1984                | 8.33 (–2.18, 18.84)  | 10.03  |
| Rask       | 1996                | 16.00 (1.16, 30.84)  | 9.20   |
| Sonnenblick| 1989                | 9.50 (3.27, 15.73)  | 10.65  |
| Takeshita  | 2010                | 45.00 (15.60, 74.40) | 6.20   |
| Zalin      | 1984                | 437.63 (59.71, 815.55) | 0.08  |
| Overall (I–squared = 96.9%, p = 0.000) | | 19.03 (7.97, 30.09) | 100.00|

NOTE: Weights are from random effects analysis.
Figure S5. Proportion of patients with thiazide-induced hyponatremia who reported fatigue.

Proportion meta-analysis plot [random effects]

Proportion meta-analysis plot [random effects]

Figure S6. Proportion of patients with thiazide-induced hyponatremia who reported dizziness.
Figure S7. Proportion of patients with thiazide-induced hyponatremia who reported confusion.

Proportion meta-analysis plot [random effects]

- Aaseth 2001: 0.333 (0.008, 0.906)
- Ambrosi 2004: 0.667 (0.094, 0.992)
- Ashraf 1981: 0.286 (0.037, 0.710)
- Bain 1966: 0.500 (0.013, 0.987)
- Bayer 1966: 0.636 (0.407, 0.828)
- Booker 1984: 0.833 (0.359, 0.996)
- Chapman 2002: 0.155 (0.085, 0.250)
- Chow 2004: 0.175 (0.127, 0.231)
- Friedman 1989: 0.545 (0.234, 0.833)
- Hung 2002: 0.143 (0.004, 0.579)
- Johnston 1989: 0.333 (0.008, 0.906)
- Kalikama 2002: 0.333 (0.008, 0.906)
- Mathew 1990: 0.241 (0.139, 0.372)
- Oles 1984: 1.000 (0.292, 1.000)
- Pinnock 1978: 1.000 (0.398, 1.000)
- Rask 1996: 0.667 (0.094, 0.992)
- Rosner 2004: 0.500 (0.013, 0.987)
- Shapiro 2010: 0.708 (0.582, 0.814)
- Sharabi 2002: 0.167 (0.115, 0.229)
- Van Wijngaarden 2010: 0.500 (0.013, 0.987)
- Yong 2011: 0.545 (0.234, 0.833)
- Zalin 1984: 0.250 (0.032, 0.651)
- combined: 0.443 (0.328, 0.561)
Figure S8. Proportion of patients with thiazide-induced hyponatremia who reported vomiting.

Figure S9. Proportion of patients with thiazide-induced hyponatremia who reported falls.
Figure S10. Proportion of patients with thiazide-induced hyponatremia who reported nausea.

Proportion meta-analysis plot [random effects]

| Study             | Proportion (95% confidence interval) |
|-------------------|--------------------------------------|
| Aaseh 2001        | 0.667 (0.094, 0.992)                 |
| Astraf 1981       | 0.571 (0.184, 0.901)                 |
| Bayer 1986        | 0.636 (0.407, 0.828)                 |
| Booker 1984       | 0.667 (0.223, 0.957)                 |
| Chapman 2002      | 0.179 (0.104, 0.277)                 |
| Friedman 1989     | 0.182 (0.023, 0.518)                 |
| Hung 2002         | 0.429 (0.099, 0.816)                 |
| Johnston 1989     | 1.000 (0.292, 1.000)                 |
| Mathew 1990       | 0.069 (0.019, 0.167)                 |
| Rask 1996         | 0.333 (0.008, 0.906)                 |
| Sharabi 2002      | 0.267 (0.204, 0.338)                 |
| Van Wijngaarden 2010 | 0.500 (0.013, 0.987)             |
| Yong 2011         | 0.273 (0.060, 0.610)                 |
| Zalin 1984        | 0.125 (0.003, 0.527)                 |
| combined          | 0.358 (0.244, 0.481)                 |
Figure S11. Proportion of patients with thiazide-induced hyponatremia who were reported to be unconscious.

Proportion meta-analysis plot [random effects]

- Aaseth 2001: 0.333 (0.008, 0.906)
- Ashraf 1981: 0.143 (0.004, 0.579)
- Bain 1986: 0.500 (0.013, 0.987)
- Booker 1984: 0.667 (0.223, 0.957)
- Chapman 2002: 0.048 (0.013, 0.117)
- Friedman 1989: 0.273 (0.060, 0.610)
- Kalkama 2002: 0.333 (0.008, 0.906)
- Mathew 1990: 0.034 (0.004, 0.119)
- Rask 1996: 0.333 (0.008, 0.906)
- Takeshita 2010: 1.000 (0.158, 1.000)
- Van Wijngaarden 2010: 0.500 (0.013, 0.987)
- combined: 0.299 (0.148, 0.476)
**Figure S12.** Proportion of patients with thiazide-induced hyponatremia who reported weakness.

Proportion meta-analysis plot [random effects]

| Study             | Proportion (95% confidence interval) |
|-------------------|--------------------------------------|
| Aaseth 2001       | 0.333 (0.008, 0.906)                 |
| Ambrosi 2004      | 1.000 (0.292, 1.000)                 |
| Bain 1986         | 0.500 (0.013, 0.987)                 |
| Bayer 1986        | 0.636 (0.407, 0.828)                 |
| Booker 1984       | 0.167 (0.004, 0.641)                 |
| Ghose 1975        | 1.000 (0.158, 1.000)                 |
| Hung 2002         | 0.143 (0.004, 0.579)                 |
| Kalima 2002       | 0.333 (0.008, 0.906)                 |
| Oles 1984         | 0.333 (0.008, 0.906)                 |
| Pinnock 1978      | 0.250 (0.006, 0.806)                 |
| Rosner 2004       | 0.500 (0.013, 0.987)                 |
| Sharabi 2002      | 0.394 (0.323, 0.470)                 |
| Van Wijngaarden 2010 | 1.000 (0.158, 1.000)             |
| Zalin 1984        | 0.125 (0.003, 0.527)                 |
| combined          | 0.446 (0.321, 0.579)                 |
Figure S13. Proportion of patients with thiazide-induced hyponatremia who reported neurological symptoms.

Proportion meta-analysis plot [random effects]

- Aaseth 2001: 0.333 (0.008, 0.906)
- Astraf 1981: 0.143 (0.004, 0.579)
- Bain 1986: 0.500 (0.013, 0.987)
- Booker 1984: 0.167 (0.004, 0.641)
- Oles 1984: 0.333 (0.008, 0.906)
- Tarssanen 1980: 0.333 (0.008, 0.906)
- Van Wijngaarden 2010: 1.000 (0.158, 1.000)
- Yong 2011: 1.000 (0.715, 1.000)
- combined: 0.510 (0.219, 0.797)
Figure S14. Proportion of patients with thiazide-induced hyponatremia who had seizures.

Proportion meta-analysis plot [random effects]

- Ashraf 1981: 0.286 (0.037, 0.710)
- Booker 1984: 0.167 (0.004, 0.641)
- Chapman 2002: 0.024 (0.003, 0.083)
- Chow 2004: 0.009 (0.001, 0.032)
- Johnston 1989: 1.000 (0.292, 1.000)
- Mathew 1990: 0.103 (0.039, 0.212)
- Oles 1984: 0.333 (0.008, 0.906)
- Rosner 2004: 0.500 (0.013, 0.987)
- Yong 2011: 0.182 (0.023, 0.518)
- Zalin 1984: 0.250 (0.032, 0.651)
- combined: 0.192 (0.083, 0.332)

Figure S15. Proportion of patients with thiazide-induced hyponatremia who had cardiovascular disease.

Proportion meta-analysis plot [random effects]

- Aaseth 2001: 0.667 (0.094, 0.992)
- Ashraf 1981: 1.000 (0.025, 1.000)
- Bain 1986: 1.000 (0.158, 1.000)
- Booker 1984: 0.167 (0.004, 0.641)
- Friedman 1989: 0.182 (0.023, 0.518)
- Hajjar 2004: 0.500 (0.013, 0.987)
- Kalkama 2002: 1.000 (0.292, 1.000)
- Mouallim 1983: 1.000 (0.398, 1.000)
- Pinrock 1978: 0.500 (0.068, 0.932)
- Shapiro 2010: 0.354 (0.239, 0.482)
- Sharabi 2002: 0.222 (0.164, 0.290)
- Tarssanen 1980: 0.333 (0.008, 0.906)
- combined: 0.487 (0.330, 0.647)
**Figure S16.** Proportion of patients with thiazide-induced hyponatremia who had diabetes mellitus.

Proportion meta-analysis plot [random effects]

- **Al Qahtani 2013** 0.723 (0.680, 0.763)
- **Chow 2004** 0.247 (0.192, 0.309)
- **Friedman 1989** 0.091 (0.002, 0.413)
- **Kalkama 2002** 0.333 (0.008, 0.906)
- **McDowell 2010** 0.042 (0.023, 0.069)
- **Rastogi 2012** 0.238 (0.219, 0.258)
- **Sharabi 2002** 0.200 (0.144, 0.266)
- **Takeshita 2010** 0.500 (0.013, 0.987)
- **Tarsanen 1980** 0.333 (0.008, 0.906)
- **combined** 0.279 (0.120, 0.475)
Figure S17. Proportion of patients with thiazide-induced hyponatremia who took hydrochlorothiazide.

Proportion meta-analysis plot [random effects]

- Asselth 2001: 0.333 (0.008, 0.906)
- Al Qahtani 2013: 0.501 (0.455, 0.547)
- Ambrosi 2004: 0.333 (0.008, 0.906)
- Ashraf 1981: 0.714 (0.290, 0.963)
- Chapman 2002: 0.013 (0.002, 0.048)
- Fenske 2009: 1.000 (0.664, 1.000)
- Fichman 1971: 0.640 (0.425, 0.820)
- Hajjar 2004: 0.500 (0.013, 0.987)
- Kalksma 2002: 0.667 (0.094, 0.992)
- Kinoshita 2011: 1.000 (0.912, 1.000)
- Lamis 2013: 1.000 (0.932, 1.000)
- Oes 1984: 1.000 (0.292, 1.000)
- Pinnock 1978: 0.250 (0.006, 0.806)
- Rosner 2004: 1.000 (0.158, 1.000)
- Sonnenblick 1989: 1.000 (0.398, 1.000)
- Takeshita 2010: 0.500 (0.013, 0.987)
- Van Wijngaarden 2010: 0.500 (0.013, 0.987)
- van Brummelen 1978: 1.000 (0.158, 1.000)
- combined: 0.683 (0.519, 0.826)
Figure S18. Proportion of patients with thiazide-induced hyponatremia who took indapamide.

Proportion meta-analysis plot (random effects)

| Study             | Proportion (95% confidence interval) |
|-------------------|-------------------------------------|
| Al Qahtani 2013   | 0.4989 (0.4527, 0.5451)            |
| Ambrosi 2004      | 0.6667 (0.5943, 0.9916)            |
| Chapman 2002      | 0.5638 (0.4802, 0.6447)            |
| Fourlanos 2003    | 0.5769 (0.5200, 0.6324)            |
| Hung 2002         | 0.7143 (0.2904, 0.9633)            |
| Jolobe 2003       | 0.0385 (0.0010, 0.1964)            |
| McDowell 2010     | 0.0268 (0.0123, 0.0502)            |
| Yong 2011         | 0.0000 (0.0000, 0.0000)            |
| combined          | 0.4721 (0.2330, 0.7183)            |
Figure S19. Proportion of patients with thiazide-induced hyponatremia who took Moduretic® (hydrochlorothiazide with amiloride).

Proportion meta-analysis plot [random effects]

Aaseth 2001 0.333 (0.008, 0.906)
Adams 1988 0.500 (0.013, 0.987)
Bain 1986 0.500 (0.013, 0.987)
Bayer 1986 0.500 (0.282, 0.718)
Canning 1988 1.000 (0.398, 1.000)
Chapman 2002 0.423 (0.342, 0.506)
Donaldson 1983 1.000 (0.398, 1.000)
Fourlanos 2003 0.372 (0.318, 0.428)
Friedman 1989 1.000 (0.715, 1.000)
Hung 2002 0.286 (0.037, 0.710)
Johnston 1989 1.000 (0.292, 1.000)
Jolobe 2003 0.385 (0.202, 0.594)
Mackay 1983 0.727 (0.390, 0.940)
Mathew 1990 0.750 (0.194, 0.994)
Pinnock 1978 1.000 (0.938, 1.000)
Rask 1996 0.750 (0.194, 0.994)
Sonnenblick 1986 1.000 (0.292, 1.000)
Tarsanen 1980 1.000 (0.292, 1.000)
Zalin 1984 1.000 (0.631, 1.000)
combined 0.733 (0.572, 0.866)
Figure S20. Proportion of patients with thiazide-induced hyponatremia who took bendroflumethiazide (bendrofluazide).

Figure S21. Proportion of patients with thiazide-induced hyponatremia who took Dyazide® (hydrochlorothiazide with triamterene).
Figure S22. Proportion of patients with thiazide-induced hyponatremia who took chlortalidone.

Figure S23. Proportion of patients with thiazide-induced hyponatremia who were also taking an Angiotensin Converting Enzyme (ACE) inhibitor.
Figure S24. Proportion of patients with thiazide-induced hyponatremia who were also taking non-steroidal anti-inflammatory drugs.

Proportion meta-analysis plot [random effects]

- Asseth 2001: 0.333 (0.008, 0.906)
- Chow 2004: 0.152 (0.108, 0.206)
- Kalksma 2002: 0.333 (0.008, 0.906)
- Oles 1984: 0.333 (0.008, 0.906)
- Rastogi 2012: 0.339 (0.317, 0.361)
- Rosner 2004: 1.000 (0.158, 1.000)

Figure S25. Proportion of patients with thiazide-induced hyponatremia who were also prescribed a non-thiazide diuretic.

Proportion meta-analysis plot [random effects]

- Ambrosi 2004: 0.333 (0.008, 0.906)
- Coenraad 2003: 0.333 (0.008, 0.906)
- Kalksma 2002: 1.000 (0.292, 1.000)
- Mouallem 1983: 1.000 (0.398, 1.000)
- Rastogi 2012: 0.201 (0.183, 0.221)

combined: 0.576 (0.190, 0.913)
Figure S26. Proportion of patients with thiazide-induced hyponatremia who were also taking antidepressants.

Figure S27. Proportion of patients with thiazide-induced hyponatremia who were also taking potassium supplements.
**Figure S28.** Proportion of patients with thiazide-induced hyponatremia who were also taking angiotensin II receptor blockers.

Proportion meta-analysis plot [random effects]

- **Kinoshita 2011**: 1.000 (0.912, 1.000)
- **Rastogi 2012**: 0.112 (0.097, 0.127)
- **Takeshita 2010**: 0.500 (0.013, 0.987)
- **combined**: 0.589 (0.001, 0.955)

Proportion (95% confidence interval)
Laboratory characteristics

**Figure S29.** Summary of mean concentration of serum sodium in patients with thiazide-induced hyponatremia (mM).

| Authorship       | Year of publication | ES (95% CI)     | % Weight |
|------------------|---------------------|-----------------|----------|
| Aaseth           | 2001                | 110.00 (109.34, 110.66) | 2.84     |
| Ambrosi          | 2004                | 113.33 (110.72, 115.94) | 2.78     |
| Ashraf           | 1981                | 105.00 (99.91, 109.19) | 2.62     |
| Bain             | 1986                | 113.00 (110.06, 115.94) | 2.77     |
| Bayer            | 1986                | 126.00 (124.78, 127.22) | 2.83     |
| Booker           | 1984                | 111.17 (105.39, 116.95) | 2.57     |
| Canning          | 1988                | 116.00 (107.20, 124.80) | 2.29     |
| Chow (Female)    | 2004                | 114.00 (112.75, 115.25) | 2.83     |
| Chow (Male)      | 2004                | 117.00 (115.07, 118.93) | 2.81     |
| Clayton          | 2006                | 119.44 (118.09, 122.79) | 2.75     |
| Coenraad         | 2003                | 124.33 (117.05, 131.61) | 2.44     |
| Donaldson        | 1983                | 130.00 (128.90, 131.10) | 2.76     |
| Fenske           | 2009                | 121.00 (111.20, 130.80) | 2.19     |
| Fichman          | 1971                | 108.12 (106.08, 110.16) | 2.80     |
| Friedman         | 1989                | 119.18 (116.35, 122.01) | 2.77     |
| Hajjar           | 2004                | 129.00 (127.05, 130.95) | 2.81     |
| Hung             | 2002                | 108.90 (105.74, 112.06) | 2.76     |
| Hwang            | 2010                | 118.00 (114.86, 121.14) | 2.76     |
| Johnston         | 1989                | 106.66 (88.88, 124.44) | 1.44     |
| Kalksma          | 2002                | 111.00 (106.93, 115.07) | 2.70     |
| Kinoshita        | 2011                | 114.79 (112.30, 117.28) | 2.79     |
| Mackay           | 1983                | 126.73 (124.24, 129.22) | 2.79     |
| Mathow           | 1990                | 118.48 (116.35, 120.61) | 2.90     |
| McDowell         | 2010                | 128.06 (127.79, 128.33) | 2.84     |
| Musch            | 2001                | 126.00 (123.75, 128.25) | 2.80     |
| Oles             | 1984                | 119.67 (109.92, 129.42) | 2.19     |
| Pincock          | 1978                | 114.67 (111.21, 118.13) | 2.74     |
| Rask             | 1996                | 117.00 (113.55, 120.45) | 2.74     |
| Rosner           | 2004                | 115.00 (102.26, 127.74) | 1.89     |
| Sharabi          | 2002                | 120.00 (119.12, 120.88) | 2.83     |
| Sonnenblick      | 1986                | 109.40 (107.47, 111.33) | 2.81     |
| Sonnenblick      | 1989                | 109.50 (102.64, 116.36) | 2.48     |
| Takeshita        | 2010                | 117.00 (109.17, 124.83) | 2.29     |
| Tarssanen        | 1980                | 112.00 (104.46, 119.54) | 2.42     |
| Thulesen         | 1980                | 111.50 (108.56, 114.44) | 2.77     |
| VanWijngaarden   | 2010                | 110.00 (108.05, 111.95) | 2.81     |
| Yong             | 2011                | 110.90 (107.41, 114.39) | 2.74     |
| Zalin            | 1984                | 117.00 (112.71, 121.29) | 2.69     |
| Overall (I-squared = 99.1%, p = 0.000) | 116.43 (113.40, 119.46) | 100.00   |

**Note:** Weights are from random effects analysis.
Figure S30. Summary of mean concentration of serum potassium in patients with thiazide-induced hyponatremia (mM).

| Authorship | Year of publication | ES (95% CI) | % Weight |
|------------|---------------------|-------------|----------|
| Asseth     | 2001                | 2.97 (2.30, 3.64) | 3.52    |
| Booker     | 1984                | 2.84 (2.37, 3.31) | 4.06    |
| Canning    | 1988                | 3.83 (3.61, 4.05) | 4.63    |
| Chow       | 2004                | 3.30 (3.20, 3.40) | 4.76    |
| Clayton    | 2006                | 3.69 (2.74, 4.64) | 2.77    |
| Fenske     | 2009                | 3.80 (3.28, 4.32) | 3.93    |
| Fichman    | 1971                | 2.88 (2.70, 3.06) | 4.67    |
| Hung       | 2002                | 3.40 (2.53, 4.27) | 2.96    |
| Hwang      | 2010                | 3.50 (3.19, 3.81) | 4.44    |
| Johnston   | 1989                | 3.00 (2.15, 3.85) | 3.02    |
| Kalksma    | 2002                | 2.73 (2.56, 2.90) | 4.69    |
| McDowell   | 2010                | 4.14 (4.07, 4.21) | 4.78    |
| Musch      | 2001                | 3.50 (3.23, 3.77) | 4.53    |
| Oles       | 1984                | 2.90 (2.32, 3.48) | 3.76    |
| Pinnock    | 1978                | 2.95 (2.85, 3.05) | 4.77    |
| Rask       | 1996                | 3.43 (2.81, 4.05) | 3.85    |
| Rosner     | 2004                | 3.30 (2.51, 4.09) | 3.18    |
| Sharabi    | 2002                | 3.80 (3.70, 3.90) | 4.76    |
| Sonnenblick| 1986                | 3.70 (3.48, 3.92) | 4.62    |
| Takeshita  | 2010                | 2.55 (2.26, 2.84) | 4.49    |
| Tarssanen  | 1980                | 3.35 (2.46, 4.24) | 2.93    |
| Thuesen    | 1980                | 3.15 (2.07, 4.23) | 2.46    |
| Van Wilgaarden | 2010              | 3.20 (2.42, 3.78) | 3.76    |
| Yong       | 2011                | 2.80 (2.45, 3.15) | 4.36    |
| van Brummelen | 1978              | 2.85 (2.56, 3.14) | 4.49    |
| Overall (I-squared = 96.8%, p = 0.000) | | 3.26 (3.02, 3.51) | 100.00  |

NOTE: Weights are from random effects analysis.
Figure S31. Summary of mean concentration of serum creatinine in patients with thiazide-induced hyponatremia (µmol/L).

| Authorship | Year of publication | ES (95% CI) | Weight | % |
|------------|---------------------|-------------|-------|---|
| Aaseth     | 2001                | 76.78 (64.14, 89.43) | 5.48 | 7.20 |
| Canning    | 1988                | 68.75 (53.18, 74.32)  | 7.35 | 7.36 |
| Chow       | 2004                | 47.00 (44.11, 49.89)  | 7.42 | 7.42 |
| Fenecke    | 2009                | 142.25 (137.15, 147.35) | 2.30 | 7.34 |
| Fichman    | 1971                | 69.08 (54.18, 75.78)  | 7.34 | 61.88 |
| Heang      | 2010                | 61.88 (52.62, 71.14)  | 7.17 | 62.00 |
| Johnston   | 1989                | 72.00 (48.48, 95.52)  | 5.92 | 97.24 |
| Kalksma    | 2002                | 103.00 (91.23, 114.77) | 7.00 | 69.98 |
| Mouallem   | 1983                | 142.25 (137.15, 147.35) | 7.35 | 61.33 |
| Musch      | 2001                | 70.82 (58.93, 82.74)  | 6.99 | 61.33 |
| Rask       | 1996                | 61.33 (59.60, 63.06)  | 7.44 | 57.24 |
| Sharabi    | 2002                | 97.24 (84.33, 110.15) | 6.91 | 48.02 |
| Takeshita  | 2010                | 68.75 (53.56, 69.44)  | 7.42 | 68.75 |
| Thuesen    | 1980                | 62.00 (45.46, 77.54)  | 6.70 | 62.00 |
| Yong       | 2011                | 76.78 (64.14, 89.43)  | 100.00 | 76.78 |

Overall (I²-squared = 98.8%, p < 0.000)

NOTE: Weights are from random effects analysis
**Figure S32.** Summary of mean serum osmolality in patients with thiazide-induced hyponatremia (mosm/kg).

| Authorship | Year of publication | ES (95% CI) | Weight | % |
|------------|---------------------|-------------|--------|---|
| Aaseth     | 2001                | 253.00 (246.76, 259.24) | 11.34  |   |
| Booker     | 1984                | 251.50 (245.06, 258.06) | 7.03   |   |
| Chow       | 2004                | 238.00 (235.64, 240.36) | 14.01  |   |
| Fidrmann   | 1971                | 242.00 (233.14, 250.86) | 9.24   |   |
| Hung       | 2002                | 237.00 (236.84, 247.16) | 8.93   |   |
| Hwang      | 2010                | 241.00 (235.34, 246.76) | 11.72  |   |
| Rask       | 1996                | 254.00 (249.34, 264.66) | 8.35   |   |
| Sonnenblick| 1986                | 241.00 (237.00, 245.00) | 13.05  |   |
| Sonnenblick| 1989                | 239.50 (234.09, 245.01) | 2.10   |   |
| Takeshita  | 2010                | 251.00 (240.65, 261.35) | 1.77   |   |
| Yong       | 2011                | 236.50 (235.60, 234.40) | 13.12  |   |
| Overall (I^2=squared = 80.3%, p = 0.000) | | 245.58 (235.64, 244.94) | 108.00 |   |

**NOTE:** Weights are from random effects analysis.
**Figure S33.** Summary of mean urinary osmolality in patients with thiazide-induced hyponatremia (mosm/kg).

| Year of publication | ES (95% CI) | Weight |
|---------------------|-------------|--------|
| Booker 1984         | 437.00 (349.76, 524.20) | 6.99   |
| Choe 2004           | 260.00 (271.13, 413.87)  | 13.24  |
| Fenske 2000         | 263.00 (215.71, 358.30)  | 8.93   |
| Fichman 1971        | 337.00 (364.60, 408.37)  | 8.00   |
| Hong 2002           | 404.00 (281.60, 526.40)  | 4.44   |
| Heang 2010          | 261.00 (239.67, 453.33)  | 9.93   |
| Johnston 1989       | 307.67 (178.19, 477.13)  | 3.32   |
| Musch 2001          | 483.00 (421.85, 544.15)  | 9.13   |
| Rask 1985           | 360.00 (141.91, 611.00)  | 1.42   |
| Rosner 2004         | 260.00 (277.60, 407.00)  | 13.64  |
| Takeshita 2010      | 490.00 (458.64, 524.41)  | 10.32  |
| Yong 2011           | 401.47 (370.31, 432.62)  | 100.00 |

NOTE: Weights are from random effects analysis

| Overall (I² = 93.9%, p < 0.000) | 401.47 (370.31, 432.62) | 100.00 |

**Figure S34.** Summary of mean concentration of urinary sodium in patients with thiazide-induced hyponatremia (mM).

| Year of publication | ES (95% CI) | Weight |
|---------------------|-------------|--------|
| Aaseth 2001         | 16.07 (11.38, 21.73)  | 11.04  |
| Booker 1984         | 84.87 (83.91, 125.62)  | 8.16   |
| Fenske 2000         | 54.00 (43.93, 64.07)   | 9.53   |
| Fichman 1971        | 37.18 (18.99, 55.37)   | 9.88   |
| Hong 2002           | 102.00 (88.56, 115.44) | 6.45   |
| Heang 2010          | 91.00 (84.29, 117.71)  | 8.74   |
| Johnston 1989       | 43.00 (7.31, 78.78)    | 7.53   |
| Musch 2001          | 64.00 (40.01, 84.00)   | 9.90   |
| Rosner 2004         | 49.50 (40.45, 68.54)   | 5.36   |
| Takeshita 2010      | 81.00 (63.88, 98.13)   | 2.53   |
| Thuesen 1980        | 50.00 (45.59, 54.41)   | 11.03  |
| Yong 2011           | 79.00 (52.35, 107.65)  | 9.95   |

**Overall (I² = 89.5%, p < 0.000) | 83.98 (46.07, 121.90) | 100.00 |
### PRISMA statement for systematic reviews

| Section/topic     | Item No | Checklist item                                                                                                                                                                                                 | Reported on page No |
|-------------------|---------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Title             |         |                                                                                                                                                                                                              |                     |
| Title             | 1       | Identify the report as a systematic review, meta-analysis, or both                                                                                                                                              | 0                   |
| Abstract          |         |                                                                                                                                                                                                              |                     |
| Structured summary| 2       | Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number | 2                   |
| Introduction      |         |                                                                                                                                                                                                              |                     |
| Rationale         | 3       | Describe the rationale for the review in the context of what is already known                                                                                                                                    | 4                   |
| Objectives        | 4       | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)                                                      | 4                   |
| Methods           |         |                                                                                                                                                                                                              |                     |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number | 5                   |
| Eligibility criteria | 6 | Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale | 5                   |
| Information sources | 7 | Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched | 5                   |
| **Search** | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated | 5 |
|------------|---|----------------------------------------------------------------------------------|---|
| **Study selection** | 9 | State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis) | 5 |
| **Data collection process** | 10 | Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators | 5 |
| **Data items** | 11 | List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made | 5 |
| **Risk of bias in individual studies** | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis | 5-6 |
| **Summary measures** | 13 | State the principal summary measures (such as risk ratio, difference in means). | 6 |
| **Synthesis of results** | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I² statistic) for each meta-analysis | 5-6 |
| **Risk of bias across studies** | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies) | 5-6 |
| **Additional analyses** | 16 | Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified | 5-6 |
| **Results** |  |  |  |
| **Study selection** | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, | 6 |
with reasons for exclusions at each stage, ideally with a flow diagram

| **Study characteristics** | 18 | For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations | 6-9 and online supplement |
|---------------------------|----|-----------------------------------------------------------------------------------------------------------------------------|---------------------------|
| **Risk of bias within studies** | 19 | Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12). | 6-9 and online supplement |
| **Results of individual studies** | 20 | For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot | 6-9 and online supplement |
| **Synthesis of results** | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency | 6-9 and online supplement |
| **Risk of bias across studies** | 22 | Present results of any assessment of risk of bias across studies (see item 15) | 6-9 and online supplement |
| **Additional analysis** | 23 | Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16) | 6-9 and online supplement |
| **Discussion** | | | |
| **Summary of evidence** | 24 | Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers) | 10-11 |
| **Limitations** | 25 | Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias) | 12-13 |
| **Conclusions** | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research | 14 |
| **Funding** | | | |
| Funding       | 27 | Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review | 14 |