# TOTAL BODY WATER IN FULL TERM AND PRETERM NEWBORNS: SYSTEMATIC REVIEW AND META-ANALYSIS

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**WHAT IS ALREADY KNOWN ON THIS TOPIC?**

* International guidance recommends that the body composition of growing preterm infants should mimic that of the fetus *in utero*.
* Total body water (TBW) is influenced by fluid status, electrolyte balance and body composition.
* Changes in TBW over time in relation to prematurity are not well understood.

**WHAT THIS STUDY ADDS**

* The typical proportion of total body water in a newborn term infant is around 74%.
* Preterm infants have a greater proportion of total body water at birth, up to 90% in the most premature neonates at 26 weeks, and this decreases with gestational age to 75% at 36 weeks.
* These findings may be of use to the clinician attempting to track changes in fluid status, electrolyte balance and body composition after birth in preterm infants.

# ABSTRACT

**Background**: Total body water (TBW) is one component of fat free mass and changes in TBW are influenced by fluid shifts (especially during transition to postnatal life), electrolyte balance and nutritional status. Normal values for term-born neonates and preterm infants at birth have not been defined in large cohorts, limiting investigation into its monitoring and use in clinical practice.

**Objective:** To systematically review the evidence base for percentage of TBW in term-born infants, quantify the effect of prematurity on TBW at birth, and describe normal progression of TBW over time in preterm infants.

**Methods:** Systematic review of Medline, Web of Science Core Collection and EBSCO-CINAHL (January 1946 to January 2020). Included articles used dilutional methods to assess TBW.

**Results:** Searches identified 2349 articles of which 22 included data suitable for analysis. Mean TBW in term-born newborns was 73.76% (95% CI 72.47% to 75.06%, 15 studies, 433 infants). Meta-regression showed that TBW was higher in preterm infants (up to 90% at 26 weeks gestation, dropping to 74% at 36 weeks corrected gestation) and was negatively correlated with gestation at birth, falling 1.44% per week (95% CI 0.63% to 2.24%, 9 studies, 189 infants). Analysis of TBW over time during the *ex-utero* growth of preterm infants was not possible due to a paucity of data.

**Conclusion:** This review defines the normal total body water percentage in term born infants and confirms and quantifies previous findings that preterm infants have a higher TBW percentage.

**PROSPERO Registration**: CRD42019111436

# Introduction

Current European1 and North American2 guidance for the nutritional care of preterm infants recommends that *ex utero* growth should match that of the fetus in utero, both in terms of weight gain and body composition. Mimicking *in utero* body composition has proven difficult to achieve in practice, with preterm infants leaving hospital lighter and shorter than their term-born counterparts.3 Importantly, preterm infants also demonstrate abnormalities of their body composition at term equivalent age (TEA).3 Specifically, they have a higher percentage of total body fat, mostly due to a relative failure to accrete lean mass.

Postnatal changes in total body water are influenced by a complex and interacting set of factors. During early adaptation there is a weight loss which is mainly mediated by loss of body water (the “preterm contraction of extracellular spaces” or PreCES).4,5 However, this is also frequently a period of cumulative nutritional deficit. Therefore, TBW changes reflect a composite of early loss of body water, subsequent abnormalities of fluid and electrolyte balance and alterations in body composition. A fuller understanding of normal values and patterns of TBW would inform investigation and clinical management of fluid status, electrolyte management and nutritional approaches.

TBW contributes to the fat free mass (FFM) component of body composition, and measurement of TBW can be used to help derive estimates of FFM (especially after early fluid loss and fluid balance disturbances), using assumptions relating to the water content of lean and fat-containing tissues.6 Therefore, a greater understanding of TBW patterns may be used as one avenue to explore and monitor elements of the derangements of body composition seen in preterm infants.

It is increasingly recognised that changes in weight are inadequate to understand these abnormalities of body composition, even when taken together with length. Observational data have demonstrated an association between greater early gains in fat-free mass (FFM) (but not fat mass) with improved neurodevelopmental markers at twelve months corrected age. These findings were robust to adjustment for known clinical confounding factors.7 Preterm infants are also prone to metabolic syndrome in later life.8,9 The mechanisms underlying this remain uncertain,10 although differences in adiposity, particularly the high fat and low lean mass pattern seen in preterm infants, have been associated with cardiometabolic risk.11

Our group has previously reviewed and summarised available methods for assessing body composition in infants.6 In short, several methods which are useful in older children and adults are impractical in the preterm infant receiving intensive care. These include MRI, air displacement plethysmography and DXA scanning. However, assessment of TBW using dilution methods is possible in this group, and involves the administration of an exogenous substance which equilibrates with the TBW pool. Levels of this substance can then be measured, and the total body water volume calculated. Early dilution studies used antipyrine, but this was later superseded due to its slight protein binding, its pharmacological effects and its metabolism.12,13 Stable isotopes of water (deuterium oxide, 18-oxygen water and tritiated water) produced values in good agreement with antipyrine experiments12 and lack the problems associated with antipyrine, although analysis is considerably more complex and expensive.

This systematic review aims to assess:

1. The normal percentage TBW of the term-born infant at birth
2. The percentage TBW of preterm infants at birth, and
3. The change in TBW as preterm infants grow and mature.

# Methods

This systematic review was prospectively registered with PROSPERO (CRD42019111436, <https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=111436>). It is reported in line with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.14

## Eligibility Criteria

The initial search strategy identified studies using a range of methods to assess total body water percentage. Results arising from different methods could not be combined in meta-analysis and so retained studies were limited to those using dilution techniques (deuterium oxide (2H2O), doubly labelled water (2H218O) or antipyrine dilution).

Studies were included if they used dilutional methods to measure total body water in term-born or preterm infants within two weeks of birth. In addition, selected studies were required to report TBW percentage and sufficient information to define gestational age and corrected gestational age of infants at the time of TBW assessment. Studies were excluded if they concerned infants with congenital abnormalities (e.g. congenital cardiac disease) or infants during the postoperative period. Animal studies, case reports, studies not published in English and review articles without primary data were also excluded.

## Search Strategy

Structured searches were made of Medline (Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions), Web of Science Core Collection and EBSCO-CINAHL (January 1946 to January 2020). Ovid MEDLINE search terms are included as Supplementary File 1. Bibliographies of selected papers were reviewed to find additional papers.

## Study Selection

Titles and abstracts were downloaded to EndNote X9 reference management software and duplicates removed. Retained titles and abstracts were uploaded to the Rayyan QCRI web application.15 Titles and abstracts were independently screened and selected by two reviewers (AY and LB), with disagreements resolved by consensus. The full text of selected articles was retrieved and reviewed for inclusion and risk of bias, and data were extracted to a custom data extraction form and compiled into a database.

## Risk of Bias Assessment

Risk of bias assessment was carried out according to the Joanna Biggs Institute checklist for Analytical Cross-Sectional Studies16.

## Data Analysis

The meta package (version 4.11-0)17 for R (version 3.6.1) was used for all analyses. Where data were reported as median and range, mean and standard deviation were estimated for comparison and meta-analysis using methods described by *Wan et al*.18 Random effects meta-analysis was selected for due to anticipated high inter-study heterogeneity (I2 >75%) and variations in the methodological approaches. Where weight for gestational age groups were listed categorically, author definition of SGA/AGA/LGA status was accepted. Where individual patient data were provided, percentile values were calculated from UK-WHO data19 (with infants described only as ‘term’ treated as being born at 40 weeks gestation). Subgroup differences were tested with the Q test for heterogeneity. Random effects meta-regression of the influence of gestational age on TBW percentage at birth of preterm infants was selected due to different methodologies and ranges of gestational ages studied. Narrative synthesis and graphical comparison were used where meta-analysis or meta-regression was not possible due to the heterogeneity of the data.

# Results

## Study Identification

Searches identified 2349 articles after deduplication. Following screening of titles and abstracts, 128 full text articles were retrieved and assessed for eligibility. From this group, 22 studies met inclusion criteria ([Fig. 1](#_Figure_1)). Fifteen papers concerned full term infants20-34 (Table 1A) and 9 concerned preterm infants24,33,35-41 (Table 1.B), with two providing information on both term-born and preterm infants24,33.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1. INFANTS BORN AT FULL TERM | | | | | | | | |
| Study | ***n*** | **Method of TBW Assessment** | **TBW Percentage (mean ±SD)** | **Birthweight (g) (mean ±SD)** | **Age at Assessment** | **Comments** | | |
| J. B. Andersen (1970)18 | 16 | Deuterium oxide dilution | 73.93 ± 4.02 | 3551 ± 622 | 2-4 hours after birth (9 hours for one infant) | Some mothers received diuretics during labour | | |
| Y. W. Brans (1983)19 | 109 | Antipyrine space | 71.72 ± 8.74 | 3600 ± 576 | 0.5 to 12 hours of life | Some infants of diabetic mothers and some macrosomic infants | | |
| G. Cassady (1971)19,20 | 26 | Antipyrine space | 72.95 ± 6.26 | 3215\* | Within 19 hours of birth | Compared normal delivery and Caesarian section | | |
| D. B. Cheek, et al. (1961)21 | 11 | Antipyrine space | 73.18 ± 2.49 | Not available | Day 3 of life | Compared diabetic and non-diabetic mothers | | |
| D. B. Cheek, et al. (1984)22 | 13 | Deuterium oxide dilution | 75.70 ± 3.20 | 2938 ± 563 | 12 hours of life | Compared preterm, term AGA and term SGA | | |
| D. B. Cheek, et al. (1982)23 | 56 | Deuterium oxide dilution | 75.79 ± 3.48 | 3931 ± 449 | 6-24 hours of life | Compared normal delivery and Caesarian section | | |
| J. R. Christian, et al. (1956)24 | 17 | Antipyrine space | 66.21 ± 5.00 | 3290 ± 330 | 6-42 hours of life |  | | |
| W. M. Clapp, et al. (1962)25 | 12 | Deuterium oxide dilution | 77.40 ± 3.10 | range: 2590-4985\* | 1-6 days of life | Compared term and preterm infants. Found lower total body water in term infants of diabetic mothers. | | |
| W. J. Cochran, et al. (1986)26 | 4 | Oxygen-18 dilution | 79.35 ± 6.38 | 2335 ± 381 | 2-3 days of life | Compared total body electrical conductivity with oxygen-18 technique | | |
| A. Llanos, et al. (1976)27 | 36 | Deuterium oxide dilution | 78.50 ± 4.62 | 2728\* | First 30 hours of life | Included AGA and SGA infants | | |
| P. J. Offringa, et al. (1990)28 | 13 | Deuterium oxide dilution | 75.10 ± 5.00 | 3456 ± 591 | First day of life |  | | |
| E. Olhager, et al. (2003)29 | 9 | Doubly labelled water | 68.10 ± 4.10 | 3895 ± 565 | 4-11 days of life | Compared term and preterm infants | | |
| M. Osler (1960)30 | 38 | Deuterium oxide dilution | 73.37 ± 5.53 | 3476 ± 523 | First day of life | Compared diabetic and non-diabetic mothers | | |
| S. C. Singhi, et al. (1995)31 | 55 | Tritiated water dilution | 73.70 ± 2.60 | 2836 ± 231 | Within 6 hours of birth | Compared term and preterm infants | | |
| C. J. Thornton, et al. (1983)32 | 18 | Antipyrine space | 73.09 ± 2.47 | 3096 ± 560 | Within 12 hours of birth | Compared normocythaemic and polycythaemic infants (no difference) | | |
|  | | | | | | | | |
| 1. PRETERM INFANTS | | | | | | | | |
| Study | ***n*** | **Mean GA (±SD)** | **Method of TBW Assessment** | **TBW Percentage (mean ±SD)** | **Birthweight (g) (mean ±SD)** | **Age at Assessment** | | **Comments** |
| Baarsma et al. (1992)33 † | 8 | 31.63 ± 3.66 | Deuterium oxide dilution | 83.24 ± 4.74 | 1683 ± 584 | 2-7 days (one infant at 15 days) |  | |
| Bauer et al. (1991)34 † | 8 | 28.00 ± 1.39†† | Deuterium oxide dilution | 79.20 ± 11.40 | 1057 ± 213 | First 12 hours of life |  | |
| Bhatia et al. (1988)35 | 17 | 34.60 ± 1.90 | Deuterium oxide dilution | 74.23 ± 4.32 | 1990 ± 82 | First 7 days of life | | |
| Cheek et al. (1984)22 † | 5 | 32.50 ± 1.74†† | Deuterium oxide dilution | 81.90 ± 2.80 | 2012 ± 397 | 12 hours of life | | Compared preterm, term AGA and term SGA |
| Hartnoll et al. (2000)36 | 42 | 27.52 ± 1.01†† | Oxygen-18 dilution | 83.39 ± 7.75†† | 1011 ± 238†† | Within 18 hours of birth | | Compared AGA and SGA infants |
| Heimler et al. (1993)37 † | 14 | 30.70 ± 2.40 | Deuterium oxide dilution | 86.60 ± 6.10 | 1473 ± 342 | Day 1 of life | |  |
| Raghavan et al. (1988)38 | 18 | 27.22 ± 2.24 | Oxygen-18 dilution | 90.65 ± 2.82 | 838 ± 161 | 1-4 days | | Validation study for bioelectrical impedance |
| Singhi et al. (1995)a39 † | 23 | 33.71 ± 1.00†† | Tritiated water dilution | 77.34 ± 16.80 | 1902 ± 242 | Within 6 hours of birth | | Tracked changes in TBW |
| Singhi et al (1995)b31 | 44 | 34.00 ± 1.57†† | Tritiated water dilution | 77.70 ± 2.60 | 1978 ± 412 | Within 6 hours of birth | | Compared term and preterm infants |

**Table 1.** Characteristics of studies included in meta-analysis of total body water percentage in term-born neonates (**A**) and in meta-regression of total body water percentage in preterm infants (**B**). \*Insufficient data to calculate or estimate mean and standard deviation. † Study measuring total body water percentage multiple times for each infant. ††Mean and standard deviation estimated from median and range using method described by *Wan et al*.18

## Total Body Water Percentage of Newborn Term Infants

Fifteen studies assessed TBW in a total of 433 newborn term infants ([Fig. 2A](#_Figure_2)). The estimated total body water percentage was 73.8% (95% confidence interval 72.47-75.06%, I2 = 90%). The antipyrine method yielded significantly lower estimates of total body water than the deuterium oxide method (random effects Q test for subgroup differences: p<0.01). There were also significant differences between the total body water estimates for SGA infants (78.3%), AGA infants (73.9%) and LGA infants (68.7%) (p<0.01) ([Fig. 2B-C](#_Figure_2)).

## Total Body Water Percentage of Preterm Infants at Birth

Mixed effects meta-regression of nine studies measuring total body water in 179 preterm newborns identified a progressive decline in percentage TBW from 85-90% between 26 and 28 weeks completed gestational age, to around 75% at 36 weeks gestational age. The estimated decline in percentage TBW was 1.44% per week (95% confidence interval 0.63-2.24%, p<0.001) (regression equation where and : ) ([Fig. 3](#_Figure_3)).

## Changes in Total Body Water as Preterm Infants Grow

Five studies measured TBW multiple times for each preterm infant (marked with † in Table 1B).24,35,36,39,41 These studies assessed 56 infants at heterogenous gestational ages and the repeated measurements were taken on different days of life ([Fig. 4A](#_Figure_4)). None of the studies gave detailed information on nutritional intake. *Baarsma et al*.35 reported two measurements each for two infants, only one of whom had a measurement taken shortly after birth. The remaining four studies did not report individual patient data but summarised the gestation at birth and the day of life when measurements were taken. *Bauer et al*.36 and *Singhi et al*.41 focused on early body composition changes as they relate to initial weight loss in preterm infants. *Cheek et al*.24 and *Heimler et al*.39 measured body composition at weekly intervals. *Cheek et al*.,24 *Heimler et al*.39 and *Singhi et al*.41 all identified that TBW percentage fell over time, with the one patient for whom early assessment was made in *Baarsma et al*.35 also exhibited a falling total body water percentage. In contrast, *Bauer et al*.36 found an initial drop in total body water followed by a rise almost back to the first measurement.

Data from these five papers were too heterogenous to perform formal meta-analysis. Data were adjusted to plot the change in total body water against the day of life. A linear regression model, weighted for the number of infants assessed in each study, confirmed that percentage TBW fell over time (1.31% per week; 95% CI 0.53-2.09%; p<0.01) ([Fig. 4B](#_Figure_4)).

# Discussion

This systematic review and meta-analysis identifies the normal percentage TBW for term-born infants. Meta-regression of studies examining percentage TBW in newborn preterm infants demonstrates a negative correlation between gestation at birth and percentage TBW. Studies with repeated measurements of preterm infants were too heterogenous for formal meta-analysis but most studies identified a fall in total body water over time.

Studies included in this systematic review were mostly performed at least twenty years ago with many being published forty to sixty years ago. This is likely to limit the generalisability of these findings to modern cohorts of preterm infants. Advances in neonatal care have led to a rapidly changing phenotype of preterm infants during this period. Despite uncertainty surrounding the impact of RDS on early fluid loss42, the surfactant era has led to significantly improved early morbidity in very preterm infants, with severe RDS now mostly limited to those born near the limits of viability. Antenatal corticosteroids have a profound influence on early fluid shifts43 and their widespread use is likely to have significantly altered the “normal” pattern of TBW changes since publication of most included studies.

## Term Infants

A strength of this review is that it includes over 400 term-born infants, whereas individual studies have rarely recruited more than 100 infants. Meta-analysis of the percentage TBW of term-born infants is limited by heterogeneity between studies. This may be due to real differences in studied populations (including demographic and nutritional differences between mothers, and differences in antenatal care) or due to differences in study protocols and methods. Furthermore, there was some variability in the timing of TBW assessment. In most cases, measurements were made within the first two days of life, but it has previously been noted that there can be rapid fluid shifts even within this limited time period.5 Subgroup analysis confirmed that measured values of TBW are influenced by the use of antipyrine compared to deuterium oxide. In addition, there were significant differences in TBW identified between SGA, AGA and LGA infants.

## Preterm Infants at Birth

This review is limited by the presence of relatively few primary research articles measuring TBW in preterm newborn infants (with only 179 subjects in this section of the review). Furthermore, data were generally reported only as the mean or median gestation at birth. Therefore, meta-analysis was performed taking this mean as the independent variable. This reduced the power and precision of the meta-regression to identify the effect of gestation at birth. This shortcoming emphasises the importance of published individual patient data.44 However, most included studies were more than two decades old and it was unfeasible to obtain individual patient data. Similar to the data for term infants, there was also heterogeneity in methods, antenatal care and timing of TBW assessment.

## Preterm Infants During Growth

There was a general paucity of data tracking TBW of preterm infants during their growth and maturation, with only 59 patients considered in this section of the meta-analysis. In addition to the sources of heterogeneity listed above, there was also very limited information on the postnatal care of these infants. It was not possible to perform formal meta-analysis of these results, although narrative synthesis identified that most papers reported a fall in percentage TBW over time. A weighted linear regression model discounting gestational age and taking week of life as the independent variable confirmed this finding. Of note, the fall in TBW of approximately 1.3% per week was just under the 1.4% figure found in the meta-regression of preterm newborn infants.

## Implications for Practice

Bearing in mind the international guidance1,2 that the body composition preterm infants at term-equivalent age should mimic that of the term-born newborn infant, the value of TBW in term-born infants identified in this study may act as a guide. However, it should be remembered that TBW reflects only one element of body composition and that derangement of fluid and electrolyte imbalance may render this comparison unreliable. This study also defines the expected TBW value for newborn preterm infants at birth in relation to their gestation. It may be expected that preterm infants would be expected to track along this trend if they are to reach a normal percentage TBW at term-corrected age.

The small amount of data pertaining to repeated measurements of TBW in preterm infants during growth makes it difficult for current *ex utero* body water changes to be assessed. Even if more such data were available, it is likely that widespread differences in medical and nutritional management of preterm infants (as well as differences in antenatal care) would frustrate attempts to meaningfully combine data to provide an overview of the *ex utero* changes occurring in the preterm infant during growth. Significant changes in body water soon after birth may mean that preterm infants deviate from the trend in TBW identified in cross-sectional assessments of newborn infants at different gestations.

Routine and reliable measurement of body composition in clinical practice currently remains out of reach. Non-invasive measures of body composition, such as bioelectrical impedance have been used but have stalled at the validation stage.45 Our group have shown that limb circumference measurements are feasible in preterm infants and demonstrate a predictable pattern of growth,46 but further work is needed to assess their clinical utility in reflecting changes in body composition.

# Conclusion

This systematic review and meta-analysis identifies potential normal values for TBW in newborn preterm and term-born infants. These findings may be useful for clinicians trying to assess changes in, fluid status, electrolyte balance, growth and body composition after birth in preterm infants. Future work should focus on tracking the body composition of preterm infants as they grow and should be contextualised by detailed monitoring of fluid management, nutritional intake and growth. Reliable and validated bedside measures of body composition in preterm infants will be required before real-time targeting of body composition can be integrated into clinical practice.

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# [Figure 1](#_Study_Identification)



**Figure 1.** PRISMA flow chart of screening and selection of studies, with reasons for exclusion based on full text review.

# [Figure 2](#_Total_Body_Water)



**Figure 2.** Total body water percentage in newborn full term infants. **A.** Forest plot with methods of TBW assessment as subgroups. **B.** Forest plot with weight for gestational age subgroups (overall test for subgroup differences: p<0.01) and **C.** Mean total body water percentage (±95% confidence interval). SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age. \*p<0.05, \*\*p<0.01.

# [Figure 3](#_Total_Body_Water_1)



**Figure 3.** Bubble plot with fitted meta-regression line of total body water percentage at birth and mean gestational age in infants included in each study. Circles are sized according to precision of the estimate, larger circles indicating greater precision. Regression equation: y=127-1.45x.

# [Figure 4](#_Changes_in_Total)



**Figure 4.A.**Total body water percentage in 58 preterm infants in 5 studies where repeated measurements of total body water were taken during their growth and maturation. Sizes of points indicate number of infants assessed. Points are plotted at the mean gestational age for infants in each study. Dashed line: linear regression line weighted for study size (slope value not significant).**B.**Change in total body water percentage in preterm infants after birth, grouped by study. Sizes of points indicate number of infants assessed. Dashed line: linear regression line weighted for study size (y=-0.13-1.31x).