

# Gone fishing in a fluid trial

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Gathering data in large randomised clinical trials (RCTs) is a burdensome task; many of the gathered data are never reported and many analyses are left unperformed. Hidden in the large amount of data from such trials are many statistically significant results<sup>1</sup> and thus treasures of potentially publishable research.<sup>2</sup>

Medical astrology, also known as iatromathematics (from Greek *iatrós* meaning doctor and *mathēmatikós* meaning mathematical), is the study of celestial bodies and their impact on the human body and disease. There are 12 astrological signs, the zodiac signs (from Greek *zōdiakós*, circle of little animals), which each represent 30° sectors of the ecliptic dating back to the late Old Babylonian Period.<sup>3</sup> In the 17th century, medical astrology was a widely accepted science, but became increasingly disfavoured in the following centuries.<sup>4</sup> Nevertheless, horoscopes are still often found in newspapers and magazines throughout the Western world. In a poll from 2008, it was found that 31% of Americans believed in astrology, and it is notable that not many more (47%) believed in Darwin's theory of evolution.<sup>5</sup>

Associations between the zodiac signs and specific diagnoses have previously been reported,<sup>6</sup> and the zodiac sign Pisces (Latin, meaning fish) was found to be strongly associated with the diagnosis of heart failure ( $P = 0.001$ ). Given the association between zodiac signs and diseases, we hypothesised, a long time after finishing a trial, that specific zodiac signs would be associated with differences in survival in an RCT.

We used data from a fluid trial and, as most fish live in a crystalloid solution (salt water), we primarily hypothesised that patients born under the sign of Pisces would have increased survival compared with patients born under other zodiac signs.

## Methods

### The 6S trial

The Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial was a multicentre, blinded RCT in which 798 intensive care patients were randomised to receive intravenous (IV) fluid resuscitation with 6% hydroxyethyl starch (HES) 130/0.42 in Ringer's acetate (Tetraspan 6%, B Braun Melsungen) or Ringer's acetate (Sterofundin ISO, B Braun).<sup>7</sup> Patients were randomised in 26 intensive care units in Denmark, Finland, Norway and Iceland between 23 December 2009 and 15 November 2011. To briefly summarise, inclusion criteria were need of fluid resuscitation

## ABSTRACT

**Objective:** To maximise the yield of existing data by assessing the effect on mortality of being born under the zodiac sign Pisces in a trial of intravenous (IV) fluids.

**Design, setting and participants:** A retrospective observational study, with no predefined hypothesis or statistical analysis plan, of 26 Scandinavian intensive care units between 2009 and 2011. Patients aged 18 years or older with severe sepsis and in need of fluid resuscitation, randomised in the Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial.

**Main outcome measure:** Ninety-day mortality.

**Results:** We included all 798 randomised patients in our study; 70 (9%) were born under the sign of Pisces. The primary outcome (death within 90 days after randomisation) occurred in 25 patients (35.7%) in the Pisces group, compared with 348 patients (48%) in the non-Pisces group (relative risk, 0.75; 95% CI, 0.54–1.03; one-sided  $P = 0.03$ ).

**Conclusions:** In a multicentre randomised clinical trial of IV fluids, being born under the sign of Pisces was associated with a decreased risk of death. Our study shows that with convenient use of statistics and an enticing explanatory hypothesis, it is possible to achieve significant findings in post-hoc analyses of data from large trials.

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and fulfilment of the criteria for severe sepsis.<sup>8</sup> Exclusion criteria included age < 18 years and receiving any form of renal replacement therapy. The 6S trial protocol was published before completion of recruitment.<sup>9</sup> Approval from the ethics committees of all participating hospitals was obtained, and written consent from patients and/or legal substitutes were obtained according to national laws.

### Our study

Ours was a post-hoc analysis of all randomised patients in the 6S trial. We used birth dates and dates from tropical astrology<sup>10</sup> to assign zodiac signs to all randomised patients. Tropical astrology dates were chosen over the dates from sidereal astrology as they are more frequently used in Western astrology.<sup>11</sup> Our primary outcome measure was 90-day mortality. The study was conducted without a written protocol and had no predefined hypothesis. We had no predefined statistical analysis plan and performed

**Table 1. Patient characteristics at baseline**

	Pisces (n = 70)	Other zodiac signs (n = 728)	P*
Median age, years (IQR)	68 (57–77)	66 (56–75)	0.52
Male, n (%)	46 (66%)	437 (60%)	0.37
Median actual body weight, kg (IQR)	71 (60–85)	78 (65–89)	0.09
Median SAPS II (IQR)	52 (41–62)	50 (39–60)	0.41
History of heart failure or MI, n (%)	10 (14%)	101 (14%)	0.86
Allocated to HES 130/0.42 group, n (%)	34 (49%)	364 (50%)	0.90

IQR = interquartile range. SAPS = Simplified Acute Physiology Score. MI = myocardial infarction. HES = hydroxyethyl starch.  
\* Using two-sided Fisher exact test or Wilcoxon rank-sum test.

additional analyses after accessing data from the trial database.

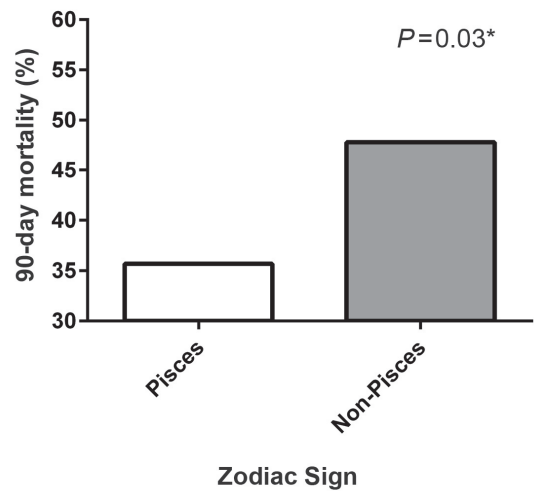
**Statistical methods**

We assessed the associations between zodiac signs and 90-day mortality using the Fisher exact test. The primary analysis was patients born under the zodiac sign Pisces compared with patients born under the 11 other zodiac signs. Secondary analyses for the remaining 11 zodiac signs were also performed. We compared 90-day mortality in a subgroup analysis of allocated fluid type (HES v Ringer’s acetate) using multiple logistic regression analysis. All statistical analyses were performed using SAS version 9.3 (SAS Institute). We used a one-tailed significance level of 0.05 to denote statistical significance for our primary analysis. We chose a one-tailed significance level because we considered a higher mortality among Pisces-born people to be highly unlikely and illogical. For all other analyses, we used a two-tailed significance level of 0.05. A high Simplified Acute Physiology Score (SAPS) II is strongly associated with increased mortality<sup>12</sup> and we noticed a higher SAPS II in the Pisces group. To account for this baseline imbalance, we performed a post-hoc multiple logistic regression analysis adjusting for the effect of being born under the sign of Pisces for SAPS II.

**Results**

All 798 randomised patients were included in our study; of these, 70 (9%) were born under the sign of Pisces (between 19 February and 20 March). With the exception of the SAPS II, there were no noteworthy baseline imbalances between patients born under the sign of Pisces and those born under other zodiac signs (Table 1).

**Figure 1. 90-day mortality in patients born under the zodiac sign Pisces, and those born under other zodiac signs combined**



\* Using one-sided Fisher exact test.

The primary outcome (death within 90 days after randomisation) occurred in 25 of 70 patients (35.7%) in the Pisces group, compared with 348 of 728 patients (48%) in the non-Pisces group (relative risk [RR], 0.75; 95% CI, 0.54–1.03; *P* = 0.03) (Figure 1). None of the other zodiac signs was associated with a difference in 90-day mortality (Table 2). In the multiple logistic regression analysis, being born under the sign of Pisces, adjusted by SAPS II at baseline, was statistically significantly associated with decreased 90-day mortality (odds ratio, 0.44; 95% CI, 0.23–0.83; *P* = 0.01).

**Subgroup analysis**

Our subgroup analysis of HES v Ringer’s acetate showed no significant difference in the effect of being born under the sign of Pisces on 90-day mortality in the HES group (RR, 0.68; 95% CI, 0.43–1.08) versus the Ringer’s acetate group (RR, 0.83; 95% CI, 0.53–1.30; *P* for heterogeneity, 0.48).

**Discussion**

We showed that being born under the zodiac sign Pisces was associated with increased survival in a multicentre RCT of IV fluids. Our results were confirmed when we adjusted for differences in disease severity at baseline. Our results fit retrospectively with the hypothesis that being born under the sign of a fish is beneficial if recruited to an IV fluid trial. Our subgroup analysis showed no significant heterogeneity of effect between allocated fluid types, but there was a

**Table 2. Secondary analyses of associations between non-Pisces zodiac signs and 90-day mortality**

Zodiac sign	N	Death within 90 days, n (%)	P*
All patients	798	373 (47%)	–
Aries (21 Mar–19 Apr)	80	40 (50%)	0.56
Taurus (20 Apr–20 May)	69	35 (51%)	0.53
Gemini (21 May–20 Jun)	76	38 (50%)	0.63
Cancer (21 Jun–22 Jul)	78	43 (55%)	0.12
Leo (23 Jul–22 Aug)	69	29 (42%)	0.45
Virgo (23 Aug–22 Sep)	55	21 (38%)	0.21
Libra (23 Sep–22 Oct)	53	23 (43%)	0.67
Scorpio (23 Oct–21 Nov)	62	26 (42%)	0.51
Sagittarius (22 Nov–21 Dec)	56	26 (46%)	1.00
Capricorn (22 Dec–19 Jan)	55	29 (53%)	0.40
Aquarius (20 Jan–18 Feb)	75	38 (51%)	0.54

\* Using two-sided Fisher exact test.

trend for a larger effect of being born under the zodiac sign Pisces in the HES group, which may indicate a type II error. A plausible explanation for an increased effect in the HES group may be the starch itself; starches in seaweed resembling land plant starches have been reported,<sup>13</sup> which may indicate that starch solutions better suit the Pisces-born. As we did not have the power to confirm the additive effect of HES, further studies are needed to establish this link. A potential interaction between intervention effect and zodiac signs (Gemini and Libra) on mortality was reported in the ISIS-2 trial<sup>14</sup> and later discussed,<sup>15</sup> but no post-hoc explanatory mechanisms were proposed.

Pisces was the only zodiac sign associated with differences in mortality. The zodiac sign Aquarius (Latin, meaning water carrier) was also an obvious candidate for increased survival in a fluid trial, but our data did not support this hypothesis. Whether the finding was due to a type II error, or because no beneficial effect of being an Aquarian actually exists, remains uncertain.

To our knowledge, we are the first to investigate the effect of zodiac signs on mortality in an RCT. Our findings were in accordance with a study on survival after allogeneic stem cell transplantation in patients with chronic myeloid leukaemia that found that being Pisces-born (pooled with five other zodiac signs, post hoc) was associated with increased survival.<sup>16</sup> Surprisingly, we could not confirm the previously reported association between history of heart failure and being born under the sign of Pisces (Table 1).<sup>6</sup> We propose two plausible explanations for this. First, it could be due to a vast difference in power; Austin and colleagues

included more than 10 million residents,<sup>6</sup> but we had data on 798 patients, which implies that we would need more than 12 000 similar fluid trials to achieve the same power. Second, selection bias may have affected the results; Austin and colleagues included an entire adult population, but we included only patients with severe sepsis, who may differ from the general population.

Basic probability implies that with a significance level of 0.05, one in every 20 analyses will by chance result in a significant difference. Because only 12 zodiac signs exist, we would not expect a significant finding by chance, and thus we do not believe our finding to be a type I error.

Our study had obvious strengths. The 6S trial was a high-quality, multicentre trial performed in several Scandinavian countries, which increases the external validity of the results, and the sample size was large enough to achieve a significant result in the primary analysis. There were also limitations to our study. Our sample size was not large enough to achieve a significant result in the subgroup analysis. All participants had severe sepsis at inclusion, so extrapolating the results to fluid trials in other settings must be done with caution. In our opinion, there is no plausible rationale for a different effect of being a Pisces in fluid trials with other patient groups.

Fluid trials are arguably not among the most frequently performed RCTs, but there are wider perspectives for this kind of research. An obvious hypothesis (to our knowledge, not yet tested) is an investigation of the effect of being born under the sign of Cancer in cancer treatment trials. Implementing findings of improved benefit of specific zodiac signs in the planning of future clinical trials, however, comes with a caveat: restricting recruitment to specific zodiac signs carries the risk of a prolonged recruitment phase, which can be detrimental to an RCT.<sup>17</sup> In the age of personalised medicine, our findings have obvious public health implications. In planning a family, prospective parents should time conception to ensure their children are born under the zodiac sign that is associated with highest survival from the conditions from which their children are likely to suffer.

## Conclusion

We found that being born under the zodiac sign Pisces was associated with improved survival in a trial of IV fluids. Our findings serve as a stellar example of how to make the most of existing data; achieving significant findings is merely a question of looking hard enough. As the hockey legend Wayne Gretzky once said: “You miss 100% of the shots you don’t take, even though there is only a 1–5% probability of scoring”.<sup>18</sup>

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## Competing interests

B Braun Melsungen delivered trial fluids to all sites in the 6S trial. Neither the funders nor B Braun had any role in the conduct of the trial or the analyses or reporting of the data. The Department of Intensive Care, Rigshospitalet, receives support for research from CSL Behring, Fresenius Kabi and Cosmed. None of the authors was born under the sign of Pisces.

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