Hospital costs during the first 5 years of life for multiples compared with singletons born after IVF or ICSI

M. M. J. van Heesch1,*, J. L. H. Evers2,3, M. A. H. B. M. van der Hoeven4, J. C. M. Dumoulin2,3, C. E. M. van Beijsterveldt5, G. J. Bonsel6,7,8, R. H. M. Dykgraaf9, J. B. van Goudoever10,11, C. Koopman-Esseboom12, W. L. D. M. Nelen13, K. Steiner14, P. Tamminga15, N. Tonch16, H. L. Torrance17, and C. D. Dirksen1

1Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Center, PO Box 5800, Maastricht 6202 AZ, The Netherlands 2Department of Obstetrics and Gynecology, Maastricht University Medical Center, PO Box 5800, Maastricht 6202 AZ, The Netherlands 3GROW, School for Oncology and Developmental Biology, Maastricht University Medical Center, PO Box 5800, Maastricht 6202 AZ, The Netherlands 4Department of Neonatology, Maastricht University Medical Center, PO Box 5800, Maastricht 6202 AZ, The Netherlands 5Department of Biological Psychology, VU University, Van der Boechorststraat 1, Amsterdam 1081 BT, The Netherlands 6Department of Obstetrics and Prenatal Medicine, Erasmus Medical Center, PO Box 2040, Rotterdam 3000 CA, The Netherlands 7Midwifery Academy Rotterdam, Roohuisenstraat 198, Rotterdam 2015 ED, The Netherlands 8Department of Public Health, Erasmus Medical Center, PO Box 2040, Rotterdam 3000 CA, The Netherlands 9Department of Pediatrics, Emma Children’s Hospital, Academic Medical Center, PO Box 22660, Amsterdam 1100 DD, The Netherlands 10Department of Pediatrics, VU University Medical Center, PO Box 7057, Amsterdam 1007 MB, The Netherlands 11Department of Neonatology, Wilhelmina Children’s Hospital, Academic Medical Center Utrecht, PO Box 85090, Utrecht 3508 AB, The Netherlands 12Department of Obstetrics and Gynecology, Radboud University Medical Center, PO Box 9101, Nijmegen 6500 HB, The Netherlands 13Department of Neonatology, Radboud University Medical Center, PO Box 9101, Nijmegen 6500 HB, The Netherlands 14Department of Neonatology, Emma Children’s Hospital, Academic Medical Center, PO Box 22660, Amsterdam 1100 DD, The Netherlands 15Academic Medical Center, Center of Reproductive Medicine, PO Box 22660, Amsterdam 1100 DD, The Netherlands 16Department of Reproductive Medicine, University Medical Center Utrecht, PO Box 85090, Utrecht 3508 AB, The Netherlands

*Correspondence address. E-mail: mirjam.van.heesch@mumc.nl

Submitted on April 25, 2014; resubmitted on January 9, 2015; accepted on February 13, 2015

STUDY QUESTION: Do in vitro fertilization (IVF) multiples generate higher hospital costs than IVF singletons, from birth up to age 5?

SUMMARY ANSWER: Hospital costs from birth up to age 5 were significantly higher among IVF/ICSI multiple children compared with IVF/ICSI singletons; however, when excluding the costs incurred during the birth admission period, hospital costs of multiples and singletons were comparable.

WHAT IS KNOWN ALREADY: Concern has risen over the long-term outcome of children born after IVF. The increased incidence of multiple births in IVF as a result of double-embryo transfer predisposes children to a poorer neonatal outcome such as preterm birth and low birthweight. As a consequence, IVF multiples require more medical care. Costs and consequences of poorer neonatal outcomes in multiples may also exist later in life.

STUDY DESIGN, SIZE, DURATION: All 5497 children born from IVF in 2003–2005, whose parents received IVF or ICSI treatment in one of five participating Dutch IVF centers, served as a basis for a retrospective cohort study. Based on gestational age, birthweight, Apgar and congenital malformation, children were assigned to one of three risk strata (low-, moderate- or high-risk).

PARTICIPANTS/MATERIALS, SETTING, METHODS: To enhance the efficiency of the data collection, 816 multiples and 584 singletons were selected for 5-year follow-up based on stratified (risk) sampling. Parental informed consent was received of 322 multiples and 293 singletons. Individual-level hospital resource use data (hospitalization, outpatient visits and medical procedures) were retrieved from hospital information systems and patient charts for 302 multiples and 278 singletons.

MAIN RESULTS AND THE ROLE OF CHANCE: The risk of hospitalization (OR 4.9, 95% CI 3.3–7.0), outpatient visits (OR 2.6, 95% CI 1.8–3.6) and medical procedures (OR 1.7, 95% CI 1.2–2.2) was higher for multiples compared with singletons. The average hospital costs
amounted to €10 018 and €2093 during the birth admission period (P < 0.001), €1131 and €696 after the birth admission period to the first birthday (not significant (n.s.)) and €1084 and €938 from the second to the fifth life year (n.s.) for multiples and singletons, respectively. Hospital costs from birth up to age 5 were 3.3-fold higher for multiples compared with singletons (P < 0.001). Among multiples and singletons, respectively, 90.8 and 76.2% of the total hospital costs were caused by hospital admission days and 8.9 and 25.2% of the total hospital costs during the first 5 years of life occurred after the first year of life.

LIMITATIONS, REASONS FOR CAUTION: Resource use and costs outside the hospital were not included in the analysis.

WIDER IMPLICATIONS OF THE FINDINGS: This study confirms the increased use of healthcare resources by IVF/ICSI multiples compared with IVF/ICSI singletons. Single-embryo transfer may result in substantial savings, particularly in the birth admission period. These savings need to be compared with the extra costs of additional embryo transfers needed to achieve a successful pregnancy. Besides costs, health outcomes of children born after single-embryo transfer should be compared with those born after double-embryo transfer.

STUDY FUNDING/COMPETING INTEREST(S): This study was supported by a research grant (grant number 80-82310-98-09094) from the Netherlands Organization for Health Research and Development (ZonMw). There are no conflicts of interest in connection with this article.

Key words: assisted reproduction / multiple pregnancy / child follow-up / hospital costs

Introduction

In vitro fertilization (IVF) has proven to be an effective treatment for infertility, and since the birth of the first IVF baby in 1978, it is now commonly used around the globe. It is well established that IVF/ICSI multiples are at increased risk of adverse events such as preterm birth and low birthweight, primarily due to the increased incidence of multiple births after IVF and ICSI (Pinborg et al., 2004a, van Heesch et al., 2014). Although offering relief to many couples suffering from involuntary childlessness, concern has risen over the long-term outcome of children born after IVF. Long-term health outcomes of IVF children are generally reassuring; however, an increased incidence of cardiovascular and metabolic risk factors has been observed among IVF offspring, which may ultimately result in cardiometabolic disease (Hart and Norman, 2013). The health outcomes of IVF offspring and its impact on hospital resources are of paramount importance to health policy makers and clinicians (Chambers et al., 2014a). Whether the differences in health outcomes of IVF multiples and singletons during the neonatal period translate into increased hospital resource use and costs beyond the neonatal period has not been substantially researched (Ericson et al., 2002; Pinborg et al., 2004b). These previous studies point to the increased use of hospital resources among multiples compared with singletons beyond the neonatal period.

The aim of the present study was to obtain an objective estimate of hospital resource utilization and hospital costs during the first 5 years of life among multiples conceived by IVF/ICSI compared with IVF/ICSI singletons. This is important to health economists and policy makers as it attaches a monetary value to what is already known about the complications associated with multiple pregnancies.

Methods

Design and study participants

All 5497 children born from IVF/ICSI between 2003 and 2005, of whom the parents received IVF/ICSI treatment in one of the five participating Dutch IVF centers, served as a base for a retrospective cohort study. These children are referred to as the ‘full sample’.

Data collection

Data of 4829 children of the full sample were successfully matched to the Netherlands Perinatal Registry (PRN; Perinale Registratie Nederland) in order to obtain neonatal data of the children. Based on their neonatal outcomes, these children were each assigned to one of three risk populations, i.e. ‘low risk’, ‘moderate risk’ or ‘high risk’ (see Fig. 1). For reasons of efficiency, retrospective data collection focused on children at risk of health problems, i.e. children of the moderate- and high-risk population. Stratified risk sampling within each risk category, with oversampling of children at risk, was used to (randomly) select 1400 children—584 singletons and 816 multiple children—for retrospective data collection of resource utilization data. These children are referred to as the ‘base sample’ (see Fig. 1). A detailed description of the data linkage procedure and risk stratification can be found elsewhere (van Heesch et al., 2014). Parents of all children of the base sample (n = 1400) were asked for informed consent for enrollment of their child(ren) in the TwinSing study. Informed consent was received from parents of 615 children (43.9%) of the base sample of which 293 children were singletons (50.2%) and 322 were multiple children (39.5%) (see Fig. 1). These children are referred to as the ‘TwinSing population’. The parents of these children consented to retrospective data collection regarding their children’s resource use based on hospital records, from birth up to age 5. Individual-level hospital resource use data were retrieved from hospital information systems and by review of patient charts. Data collection of 35 children could not be performed, because the hospital was not willing to facilitate the data collection (n = 25), hospital records could not be retrieved (n = 2) or time constraints (n = 8). These children were excluded from analysis. Hospital data were collected for 278 of 293 singletons and 302 of 322 multiple children. Incomplete hospital data were collected for 25 children, as one of the hospitals was not willing to facilitate the collection of all data. Resource use and hospital costs of these children are thus underestimated.

Outcome measures

Hospital resource utilization

The odds of being admitted to the hospital, outpatient visits and medical procedures were calculated for each period of interest (birth admission, after the birth admission to the end of the child’s first life year, second to fifth life year and from birth to fifth life year, i.e. total). Birth admission is defined as hospital admission on the day of birth. Hospital episodes that resulted in a transfer were merged with previous episodes to calculate length of hospital stay and number of admissions. When an admission spanned two time periods,
Figure 1  Flowchart of data linkage, risk stratification and selection of infants for empirical data collection.
it was allocated to the former. For each period of interest, the proportion of infants with resource use (i.e. admissions, outpatient visits and medical procedures), the costs of resource use, the average length of hospital stay and the average number of (outpatient) visits was calculated among all infants including those without resource use. If a hospital registered a consultation with a medical specialist during an admission, the consultation was counted and valued as an outpatient visit.

Hospital costs
The cost analysis was performed from the hospital perspective and included all use of hospital resources during the first 5 years of the children’s’ lives. Costs related to (mode of) delivery were not included in the analysis. Costs were derived by multiplying the resources used by its unit price and added to calculate the hospital costs of each period of interest. The cost analysis was performed according to the Dutch guidelines for cost calculations in healthcare (Hakkaart-van Roijen et al., 2010), and reference prices from the guideline were used to determine most unit prices. Cost prices of medical procedures are not included in the latest Dutch guideline, and therefore, the unit prices published in the previous version of the guideline were used (Oostenbrink et al., 2004). When a reference unit price could not be obtained from the guidelines, unit prices were obtained from the financial department of the hospital. If a child was discharged on the same day as the admission day, the reference price for day treatment was used. Reference prices for admission days depended on the type of hospital (general hospital versus academic hospital) and type of ward (general versus intensive care unit). In case of a transfer, the unit price of the most expensive hospital and/or ward was used. Telephone contacts with medical specialists were valued at half of the price of an outpatient visit. Costs were presented in 2012 Euros and were indexed to the year 2012 via consumer price indexes of Statistics Netherlands. All costs after the first year of birth were discounted at 4%.

Statistical analysis
Statistical analysis was performed using PASW Statistics version 20 (IBM Corp., Armonk, NY, USA) and Microsoft Office Excel 2010 (Microsoft Corporation, Redmond, USA). Statistical significance was defined as \( P < 0.05 \) (two-sided). For all analyses, infant was the unit of analysis, which means that each child of a multiple was included in the analyses with its own data record.

Per risk stratum, representativeness of the TwinSing population was investigated by comparing PRN registry data (i.e. gestational age, birthweight, 5-min Apgar score, small-for-gestational-age, child sex, maternal age and primiparity) of those children with the children of the overall IVF population (i.e. full sample). Student’s \( t \)-tests (parametric data) and Mann–Whitney \( U \)-tests (non-parametric data) were used to compare mean differences between groups and Pearson \( \chi^2 \)-tests to compare distributions between groups.

As a result of the stratified risk sampling, with oversampling of children at risk, the proportions of low-, moderate- and high-risk infants in the TwinSing population did not reflect the proportions in the original IVF population (i.e. full sample). Frequentist statistics on overall group level could thus not be performed. Therefore, bootstrap analysis was used to compare hospital care utilization (e.g. number of days hospitalized and number of outpatient visits) and hospital costs in multiples and singletons. It has the advantage of not relying on parametric assumptions concerning the underlying distribution. Bootstrap analysis randomly draws, with replacement, a number of samples of the original data to estimate the sample distribution of a statistic. For each simulation, the number of low-, moderate- and high-risk children was adjusted to properly reflect the ratio of low-, moderate- and high-risk children in the original population (i.e. full sample, see Fig. 2). More precisely, each simulation of multiples (302 draws) consisted of 144 draws from the low-risk population, 103 draws from moderate-risk population and 55 draws from high-risk population. Likewise, each simulation of singletons (278 draws) consisted of 245, 26 and 7 draws from, respectively, the subpopulation of low-risk, moderate-risk and high-risk singletons. To derive the distributions of hospital resource utilization and hospital costs, 5000 simulations of sampling with replacement from original data were performed. Bootstrap analyses were used to calculate bootstrapped 95% confidence intervals (CIs) of the odds ratios (ORs) or mean differences of multiples compared with singletons. Hospital costs were compared for multiples and singletons of the overall TwinSing population and within the three risk subpopulations.

Ethical approval
The current study is part of the TwinSing study, which has been reviewed and approved by the Medical Ethics Committee of the Maastricht University Medical Centre (MEC 09-4-019, date 2 November 2009).

Results
Child and parental characteristics
Hospital data were empirically collected for 302 of 322 multiple children (93.8%), of whom 63 low-risk infants, 121 moderate-risk infants and 118 high-risk infants. Among singletons, hospital data were collected for 278 children (94.9%) of whom 129 low-risk infants, 126 moderate-risk infants and 23 high-risk infants. Maternal and infant characteristics are presented in Table I. The proportion of boys was higher among multiples compared with singletons of the low-risk population (\( P < 0.01 \)). The mothers of moderate-risk multiples were significantly younger than the mothers of moderate-risk singletons (\( P < 0.05 \)). Perinatal outcomes of multiples and singletons in the separate risk categories are reported elsewhere (van Heesch et al., 2014).

Children of the TwinSing population of whom empirical data were collected were comparable with the children of the full sample, except that (i) low-risk singletons had mothers who were significantly older (34.7 versus 33.8; \( P < 0.05 \)), (ii) moderate-risk singletons had a higher 5-min Apgar score (9.4 versus 9.0; \( P < 0.05 \)), (iii) high-risk singletons had a longer gestational age (33.1 versus 31.1; \( P < 0.05 \)), (iv) low-risk multiples had a lower 5-min Apgar score (9.4 versus 9.6; \( P < 0.05 \)), (v) low-risk multiples were more often boys (65.1 versus 50.6%; \( P < 0.05 \)) and (vi) moderate-risk multiples had a lower birthweight (2388 versus 2476; \( P < 0.01 \)) compared with children of the full sample, based on PRN registry data. These differences were small and not considered clinically relevant, besides that high-risk singletons from the TwinSing population were born at a considerably longer gestational age compared with high-risk singletons from the full sample. The gestational age influences the decision of admission to a neonatal intensive care unit (NICU), which is indicated at gestational ages below 32 weeks. Therefore, hospital care utilization and hospital costs of high-risk singletons might be underestimated. To take this into account, the bootstrap estimates of high-risk singletons were corrected for gestational age, i.e. for each bootstrap simulation, the number of high-risk singletons born before and after 32 weeks of gestation was adjusted to reflect the ratio high-risk singletons born before and after 32 weeks of gestation in the full sample.

Hospital resource utilization

Hospital admission
Data on hospital admissions are summarized in Table II. More than 80% of multiples had been admitted to the hospital versus approximately half of the singletons (\( P < 0.001 \)). The majority of admissions occurred
during the first year of life, both among multiples (62.1%) and singletons (57.9%). The risk of being hospitalized directly following birth (denoted as birth admission) was significantly higher for multiples compared with singletons (OR 6.4, 95% CI 4.4–9.1). However, the risk of (re-)hospitalization was comparable for multiples and singletons after the birth admission to the first birth day (n.s.) and from the second to the fifth year of life (n.s.). Multiples spent 10.5 more days in the hospital than singletons during the birth admission ($P < 0.001$). After the birth admission, the length of stay did not differ significantly between multiples and singletons.

**Outpatient visits**

Approximately 70% of the multiples compared with less than half of the singletons visited a medical specialist in a hospital (Table III). The risk of an (outpatient) visit was significantly higher among multiples compared with singletons both during the birth admission period (OR 2.7, 95% CI 1.6–4.6), after the birth admission period to the first birthday (OR 2.8, 95% CI 2.0–3.9) and after the first year of life (OR 1.8, 95% CI 1.3–2.4). During the first year of life, the average number of (outpatient) visits was more than twice as high in multiples compared with singletons ($P < 0.001$). This discrepancy decreased with increasing child age, and the number of outpatient visits was comparable among multiples and singletons after the first year of life.

**Medical procedures**

The proportion of children who underwent at least one medical procedure in multiples and singletons was 55.2 and 43.2%, respectively ($P < 0.01$). During the birth admission period, multiples had a 4.8-fold increased risk of a medical procedure (OR 4.8, 95% CI 3.0–7.9) and the number of procedures was significantly higher (1.6 versus 0.3, $P < 0.001$) (Table III). However, medical procedures were not more often observed among multiples compared with singletons after the birth admission period. Specific procedures are listed in Supplementary Table SI. The majority of the performed procedures were diagnostic or minor surgical procedures. Approximately 65 and 70% of the total number of surgical procedures in multiples and singletons consisted of minor surgery, such as ear surgery and mouth, nose and throat surgery. X-ray and ultrasonography comprised ~84 and 75% of the total number of diagnostic procedures in multiples and singletons, respectively.

**Hospital costs**

The majority of hospital costs occurred during the birth admission period among both multiples (81.9%) and singletons (56.2%) (see Fig. 3). The average hospital costs of the birth admission period amounted to €10,018 and €2093 for multiples and singletons, respectively ($P < 0.001$). The hospital costs amounted to €1131 and €696 from the birth admission period to the first birthday (n.s.) and €1084 and €938 from the...
### Table 1: Maternal and infant characteristics of IVF/ICSI multiples and singletons, per risk strata.

<table>
<thead>
<tr>
<th></th>
<th>Low risk</th>
<th>Moderate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Singletona</td>
<td>Multiplea</td>
<td>Multipleb</td>
</tr>
<tr>
<td>Number of children</td>
<td>129</td>
<td>63</td>
<td>34</td>
</tr>
<tr>
<td>Infant characteristicsa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)d</td>
<td>45.0</td>
<td>65.1**</td>
<td>73.5**</td>
</tr>
<tr>
<td>Gestational age (weeks)e</td>
<td>40.1</td>
<td>38.1****</td>
<td>38.1****</td>
</tr>
<tr>
<td>Birthweight (kg)e</td>
<td>3427</td>
<td>2765****</td>
<td>2727****</td>
</tr>
<tr>
<td>5-min Apgar scoree</td>
<td>9.6</td>
<td>9.4*</td>
<td>9.4</td>
</tr>
<tr>
<td>Congenital malformation (%)d</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>NICU admission (%)d</td>
<td>0.8</td>
<td>1.6</td>
<td>2.9</td>
</tr>
<tr>
<td>Maternal characteristicsb,f</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)c</td>
<td>34.7</td>
<td>33.7</td>
<td>33.6</td>
</tr>
<tr>
<td>Low socioeconomic status (%)d</td>
<td>31.8</td>
<td>22.2</td>
<td>23.5</td>
</tr>
<tr>
<td>Dutch nationality (%)d</td>
<td>95.3</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Nulliparous (%)d</td>
<td>69.0</td>
<td>58.7</td>
<td>61.8</td>
</tr>
<tr>
<td>Double-embryo transfer (%)d,g</td>
<td>77.7</td>
<td>100.0***</td>
<td>100.0**</td>
</tr>
<tr>
<td>Delivery in hospital (%)d</td>
<td>81.4</td>
<td>100.0***</td>
<td>100.0**</td>
</tr>
<tr>
<td>Mode of delivery, cesarean section (%)d</td>
<td>17.2</td>
<td>60.3***</td>
<td>55.9***</td>
</tr>
<tr>
<td>Resource utilization during first 5 years of life in:h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average number of hospitals visited per childd</td>
<td>0.59</td>
<td>0.90***</td>
<td>0.97**</td>
</tr>
<tr>
<td>General hospital (%)</td>
<td>45.7</td>
<td>66.7**</td>
<td>67.6**</td>
</tr>
<tr>
<td>Academic hospital (%)</td>
<td>11.6</td>
<td>17.5</td>
<td>20.6</td>
</tr>
</tbody>
</table>

---

*a* Unit of analysis: child.

*b* Unit of analysis: mother.

*c* *t*-test for equality of means.

*d* Pearson’s X² test.

*e* Mann–Whitney U test.

*f* Mothers of multiples may have given birth to children who were assigned to different risk categories.

*g* Missing data with respect to embryo transfer of 70 mothers (low-risk singleton: n = 35; moderate-risk singleton: n = 30; high-risk singleton: n = 5).

*h* Incomplete hospital data collection for 25 children (low-risk singleton: n = 1; moderate-risk singleton: n = 6; high-risk singleton: n = 2; low-risk multiple: n = 2; moderate-risk multiple: n = 5; high-risk multiple: n = 9).
### Table II  Hospital resource utilization among IVF/ICSI multiples and singletons (hospital admissions)*.

<table>
<thead>
<tr>
<th>Multiples&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Children (%)</th>
<th>No. of admissions</th>
<th>LOS</th>
<th>Costs</th>
<th>Singletons</th>
<th>Children (%)</th>
<th>No. of admissions</th>
<th>LOS</th>
<th>Costs</th>
<th>OR (95% CI)</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth admission</td>
<td>80.5</td>
<td>0.80</td>
<td>13.22</td>
<td>€9831</td>
<td>39.8</td>
<td>0.40</td>
<td>2.73</td>
<td>€2040</td>
<td>6.4 (4.4–9.1)***</td>
<td>0.41 (0.34–0.48)***</td>
<td>10.48 (8.92–12.20)***</td>
</tr>
<tr>
<td>Birth admission to 1 year</td>
<td>14.0</td>
<td>0.20</td>
<td>1.41</td>
<td>€831</td>
<td>10.8</td>
<td>0.17</td>
<td>0.62</td>
<td>€403</td>
<td>1.4 (0.8–2.1)</td>
<td>0.03 (–0.06–0.12)</td>
<td>0.79 (–0.02–1.94)</td>
</tr>
<tr>
<td>2nd–5th life year</td>
<td>29.8</td>
<td>0.61</td>
<td>1.04</td>
<td>€447</td>
<td>23.9</td>
<td>0.41</td>
<td>0.78</td>
<td>€397</td>
<td>1.4 (0.9–2.0)</td>
<td>0.20 (0.00–0.43)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.25 (–0.32–0.87)</td>
</tr>
<tr>
<td>Total</td>
<td>83.3</td>
<td>1.61</td>
<td>15.66</td>
<td>€11110</td>
<td>51.4</td>
<td>0.98</td>
<td>4.14</td>
<td>€2840</td>
<td>4.9 (3.3–7.0)***</td>
<td>0.63 (0.37–0.93)***</td>
<td>11.52 (9.42–13.91)***</td>
</tr>
</tbody>
</table>

*Results based on bootstrap analysis; bootstrap estimates of high-risk singletons were corrected for gestational age (<32 weeks; ≥32 weeks of gestation).

<sup>b</sup>Unit of analysis: child.

### Table III  Hospital resource utilization among IVF/ICSI multiples and singletons (outpatient visits and medical interventions)*.

<table>
<thead>
<tr>
<th>Multiples&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Children (%)</th>
<th>No. of visits/ interventions</th>
<th>Costs</th>
<th>Singletons</th>
<th>Children (%)</th>
<th>No. of visits/ interventions</th>
<th>Costs</th>
<th>OR (95% CI)</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth admission</td>
<td>16.7</td>
<td>0.26</td>
<td>€22</td>
<td>7.3</td>
<td>0.11</td>
<td>€9</td>
<td>2.7</td>
<td>1.6–4.6***</td>
<td>0.15 (0.05–0.25)**</td>
</tr>
<tr>
<td>Birth admission to 1 year</td>
<td>54.4</td>
<td>2.52</td>
<td>€193</td>
<td>30.0</td>
<td>1.14</td>
<td>€98</td>
<td>2.8</td>
<td>2.0–3.9***</td>
<td>1.37 (0.91–1.85)***</td>
</tr>
<tr>
<td>2nd–5th life year</td>
<td>56.3</td>
<td>4.51</td>
<td>€352</td>
<td>42.1</td>
<td>3.38</td>
<td>€261</td>
<td>1.8</td>
<td>1.3–2.4***</td>
<td>1.12 (–0.02–2.38)</td>
</tr>
<tr>
<td>Total</td>
<td>69.8</td>
<td>7.28</td>
<td>€567</td>
<td>47.6</td>
<td>4.64</td>
<td>€368</td>
<td>2.6</td>
<td>1.8–3.6***</td>
<td>2.64 (1.16–4.23)***</td>
</tr>
<tr>
<td>Medical interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth admission</td>
<td>21.8</td>
<td>1.59</td>
<td>€165</td>
<td>5.7</td>
<td>0.35</td>
<td>€42</td>
<td>4.8</td>
<td>3.0–7.9***</td>
<td>1.24 (0.67–1.90)***</td>
</tr>
<tr>
<td>Birth admission to 1 year</td>
<td>27.0</td>
<td>0.73</td>
<td>€107</td>
<td>22.3</td>
<td>0.71</td>
<td>€196</td>
<td>1.3</td>
<td>0.9–1.9</td>
<td>0.04 (–0.40–0.48)</td>
</tr>
<tr>
<td>2nd–5th life year</td>
<td>41.1</td>
<td>2.05</td>
<td>€284</td>
<td>35.2</td>
<td>1.75</td>
<td>€280</td>
<td>1.3</td>
<td>0.9–1.8</td>
<td>0.30 (–0.42–1.03)</td>
</tr>
<tr>
<td>Total</td>
<td>55.2</td>
<td>4.36</td>
<td>€557</td>
<td>43.2</td>
<td>2.80</td>
<td>€519</td>
<td>1.7</td>
<td>1.2–2.2**</td>
<td>1.56 (0.39–2.81)**</td>
</tr>
</tbody>
</table>

<sup>*P < 0.05; **P < 0.01; ***P < 0.001.</sup>

<sup>b</sup>Results based on bootstrap analysis; bootstrap estimates of high-risk singletons were corrected for gestational age (<32 weeks; ≥32 weeks of gestation).

<sup>c</sup>Unit of analysis: child.
Hospital costs were 3.3-fold increased for multiples (per child) compared with singletons during the first 5 years of life, resulting in a cost difference of €8506. Among multiples, 90.8% of the costs were attributable to hospitalization, 4.6% to outpatient visits and 4.6% to medical procedures. Among singletons, the corresponding figures were 76.2, 9.9 and 13.9%. Analyses performed to evaluate the co-dependency of data of multiples did not alter the significance levels of the comparison of hospital costs of multiples and singletons during any of the periods of interest when using pregnancy as unit of analysis. The only exception being that multiples incurred higher costs of outpatient visits compared with singletons during the second to fifth life year when pregnancy was used as the unit of analysis. The only exception being that multiples incurred higher costs of outpatient visits compared with singletons during the second to fifth life year when using child as unit of analysis.

More resource utilization and higher hospital costs were observed among high-risk infants compared with moderate-risk and low-risk infants (Supplementary Table SII and SIII). Additional analyses comparing multiples and singletons within the three risk groups showed that multiple birth children were associated with higher hospital costs in the low-risk population (costs difference: €1891, \( P < 0.001 \)) and similar costs in the moderate-risk population (cost difference: −€3869, n.s.) and high-risk population (−€16,476, n.s.) compared with singleton births.

**Discussion**

This study shows the increased use of hospital resources and hospital costs of IVF/ICSI multiples compared with IVF/ICSI singletons during the first 5 years of life. Hospital admissions, outpatient visits and medical procedures were more frequent among multiples compared with singletons, resulting in 3.3-fold higher hospital costs among multiples. Approximately 97.2% of the cost difference was attributable to hospital admissions, 2.3% to outpatient visits and 0.4% to medical procedures. The average hospital cost of a multiple was €12,233 per child, during the first 5 years of life. Although high-risk multiples represent less than one-fifth of the total population of multiples, they incurred almost two-thirds of the costs of multiples. The average hospital costs of a singleton up to age 5 was €3727. Although low-risk singletons represent 88.3% of the total number of singletons, they incurred only one-third of the hospital costs. In contrast, high-risk singletons represent only 2.3% of all singleton births but incurred more than one-third of the hospital costs.

Hospital costs applied mainly to the first period of life; 81.9 and 57.6% of the costs of hospital care were incurred during the birth admission period and 91.1 and 74.7% during the first life year among multiples and singletons, respectively.

The bulk of the cost difference between multiple and singleton birth children is explained by the high-risk population (77.1%), although high-risk infants represent only 8.3% of the total IVF population. The remainder is explained by the moderate-risk (19.4%) and low-risk population (3.4%), which represent, respectively, 18.6 and 73.2% of the total IVF population.

Taken together the results of the present study indicate that multiples born after IVF have an increased use of hospital care resources compared with singletons, during the first 5 years of life. When excluding the costs borne during the birth admission, hospital costs of multiple and singleton birth children were comparable. This is in agreement with previous published observations that the main increased utilization of healthcare by multiples occurs during the birth admission period (Leslie et al., 1998; Ericson et al., 2002; Henderson et al., 2004; Kallen et al., 2005; Chambers et al., 2014b). In the current study, almost one out of four IVF/ICSI children underwent a surgical procedure. However, it is
reassuring that more than two-thirds of the total number of surgical procedures were minor operations, e.g., ear surgery and mouth, nose, and throat surgery. This is in accordance with a study from Denmark (Pinborg et al., 2004b), although the number of surgical procedures in our study is somewhat lower. Likewise, the main diagnoses leading to hospitalization in multiples and singletons were middle ear, upper respiratory tract and gastrointestinal infections in a study from Finland (Koivurova et al., 2007), reflecting the benign nature of health problems in both IVF multiples and singletons. Reported costs in our study were higher than those reported elsewhere; however, the generalizability of the findings is limited by differences in healthcare systems and cost prices across nations.

A large part of the literature on preterm infants is also relevant to IVF/ICSI multiple births, as they are more often born prematurely than IVF/ICSI singletons. In the current study, more than half of the multiples were preterm births (<37 weeks of gestation) compared with 8% of the singletons. It has been shown that gestational age at birth is the strongest predictor of hospital cost during the first 5 years of life (Pietz et al., 2003). Research findings indicated that >92% of the incremental costs per preterm birth were caused during the neonatal period (Mangham et al., 2009). After the age of 2, the cost per preterm birth infant was comparable with the cost per term infant (Mangham et al., 2009).

In the current study, nearly half of the multiples were moderate preterm (32-33.56 weeks of gestation) or late preterm births (34.5-36.1 weeks of gestation) compared with only a small portion of the singletons. Some studies even suggest that moderate preterm and late preterm births are at risk of adverse growth (Pietz et al., 2004; Blackwell et al., 2005), neuropsychological (Holmqvist et al., 1987; Pietz et al., 2004), educational (Huddy et al., 2001) and behavioral (Huddy et al., 2001) outcomes and higher costs (Pietz and Khan, 2012) and that they contribute to the largest share of costs since they account for the vast majority of preterm births (Underwood et al., 2007; Mangham et al., 2009; Pietrou and Khan, 2012). In the current study, ~85.3 and 83.5% of preterm multiples and singletons were moderate or late preterm births.

A strength of the current study is that we applied a systematic and efficient approach to data collection in a representative cohort of IVF/ICSI children, by assigning children to a ‘low-risk’, ‘moderate-risk’ or ‘high-risk’ category. Data collection focused on children from the moderate- and high-risk population. The downside is that frequentist statistical comparison between multiples and singletons was not possible on an overall group level. Hence, data of multiples and singletons were compared with bootstrap analysis.

Singletons of the high-risk population of whom hospital data were collected were not representative of the original population of high-risk IVF/ICSI singletons with respect to gestational age. Therefore, bootstrap estimates of high-risk singletons were adjusted for gestational age. As a result, the average hospital costs of a high-risk singleton increased by €13,431 from €46,135 without correction for gestational age to €59,566 with correction for gestational age. As the proportion of high-risk singletons among the total population of singletons is low (2.3%), the correction did not have a profound influence on the overall comparison between multiples and singletons. The average hospital costs of a singleton increased by €297 from €3,430 to €3,727. Analyses without correction for gestational age did not alter the conclusions of the present study.

The subpopulation of high-risk singletons consisted of 23 infants in whom hospital data were collected. The small number of infants might have led to insignificant results of the comparison of multiple (n = 118) and singleton (n = 23) children in the high-risk population, due to lack of statistical power.

Another limitation of the current study is its focus on hospital costs only. Adopting a broader perspective would probably have increased the cost difference between multiples and singletons. Two systematic literature reviews have revealed that preterm birth, which is prevalent among multiples, can result in substantial costs outside the hospital through its burden on social services, special education, on families and caregivers of the infant and on society (Pietrou et al., 2001; Pietrou et al., 2011).

IVF treatment accounts for only a small portion of public health expenditure (Chambers et al., 2007), but the hidden cost of fertility treatment is the high incidence of multiple births (Ledger et al., 2006). Despite the trend to transfer fewer, and in particular just one, embryo into the uterus during IVF treatment, current figures indicate that multiple births still account for one-fifth of all births after IVF/ICSI in Europe (Kupka et al., 2014). The additional hospital costs of an IVF/ICSI multiple child over a singleton amount approximately to €8,399 during the first 5 years of life. If all Dutch multiple births born in 2013 after IVF had been born as singletons, approximately €1.6 million would have been saved on hospital care during the first five life years of the children. To this should be added the costs outside the hospital. Savings to the healthcare sector and society by reducing multiple births through elective single-embryo transfer strategies could be used to fund additional IVF or ICSI treatment cycles needed in order to achieve similar pregnancy rates to those after double-embryo transfer (Ericson et al., 2002). This argument has already been used to change funding policies in some countries (Gordts et al., 2005; Bissonnette et al., 2011; Chambers et al., 2011; Kutlu et al., 2011). This study focused on the costs of hospital care of multiples and singletons born after IVF. The costs of achieving a pregnancy should also be considered in policy decisions regarding the number of embryos to transfer. Often parents desire to have more than one child. It is known that parents of IVF/ICSI singletons more often opt for another IVF treatment cycle. The costs of the additional IVF treatments needed to create a complete family ideally should be incorporated in analyses comparing embryo transfer strategies. Also, not only costs but also health outcomes of IVF/ICSI multiples and singletons should be considered in decisions regarding embryo transfer strategies as costs alone cannot be the sole reason for reducing the number of multiple births by single-embryo transfer.

Acknowledgements

The authors thank Sanne Joosten for her assistance with the data collection and Fons Kessels for his assistance in the statistical analysis of the data.

Authors’ roles

All authors participated in designing the study. C.D. is the project leader of the TwinSing study. M.v.H., M.v.d.H., J.D., R.D., J.v.G., C.K., W.N., K.S., P.T., N.T. and H.T. contributed to the acquisition of data. M.v.H. performed data linkage, analyzed the data and wrote the manuscript. All authors revised the manuscript and read and approved the final version of the manuscript for publication.
Funding
This study was supported by a research grant (grant number 80-82310-98-09094) from the Dutch Organization for Health Research and Development (ZonMw).

Conflict of interest
None declared.

References


