# Regional Variations in Trends for Multiple Births: A Population-Based Evaluation in France, 1972–2003

Babak Khoshnood and Béatrice Blondel

*INSERM, UMR S149, IFR 69, Epidemiological Research Unit on Perinatal and Women's Health, Villejuif, France; Université Pierre et Marie Curie-Paris6, Paris, France*

The aim of the study was to assess, using population-based data, trends and regional variations in multiple births during the period of increasing use and changes in practice patterns for infertility treatments. National data for 24,554,977 births (live births and stillbirths) were used, including 569,423 twins during the period 1972 to 2003, and 14,599 triplets for 1984 to 2003. Statistical analyses included age-adjusted hierarchical logistic regression models for twin births and separate analyses for triple, same-sex, and different-sex twin births. Due to confidentiality considerations, the only variable available for adjustment was maternal age. Regional-level variations were estimated using median odds ratios based on random-intercept hierarchical logistic regression models. Overall, twin births increased from 18.1 per 1000 births (95% confidence interval [CI] 17.9–18.2) in 1972 to 1975 to 29.9 per 1000 (95% CI 29.7–30.1) in 2000 to 2003. Twin births increased progressively across all regions, whereas triple births reached a peak in the early 1990s and decreased thereafter. Trends for both twin and triple births varied significantly across regions. Both trends and regional variations were greater for different-sex as compared with same-sex twin births. Regional variations in the proportion of multiple births increased in the case of twin births and decreased for triple births. Differences in multiple births at the regional level in France were comparable to country-level differences observed across several western and northern European countries. Regional differences in multiple births need to be monitored and used to inform policies aimed at regulating the use of infertility treatments.

Along with increasing use of infertility treatments, and trends towards delayed childbearing (Breart et al., 2003), multiple births, with their attendant risks and costs, have increased substantially in industrialized countries over the past three decades (Kaprio & Marttila, 2005: Macfarlane & Blondel, 2005). Trends for multiple births are known to vary significantly across countries. The reasons for these differences are incompletely understood but they are thought to reflect in part differences in the supply of, and/or practices related to, infertility treatments (Andersen et al., 2005). On the other hand, few studies (Allen, 1988; Fellman & Eriksson, 2005; Martin & Park, 1999) have examined regional differences in multiple births for a given country using recent population-based data.

In France, regional differences are known to exist in both the availability and use of health services (Lucas & Tonnellier, 1996), and in health outcomes, including those related to perinatal health (Blondel et al., 2005). These differences are not entirely accounted for but are related in part to general socioeconomic characteristics of the regions (Institut National de la Statistique et des Études Économiques [INSEE], 2003). Regional differences in health services and outcomes persist in France despite a national system of health insurance and the existence of national policy guidelines for availability, quality and reimbursement of health services. This is especially the case for those services related to pregnancy and perinatal healthcare, including those related to infertility treatments.

Geographical variations have been documented in both the 'baseline' twinning rates and in the long-term trends for twinning prior to the introduction of infertility treatments (Hemon et al., 1981). However, regional differences in multiple births in France have not been examined using recent data corresponding to the era following the introduction of infertility treatments. Evaluation of such differences, and how they may have changed over time, can provide useful information for evaluating the impact of possible regional differences in access to (demand and supply of) infertility treatments. Regional differences in multiple births could also be of interest as part of needs assessment for obstetric and neonatal care, and in the evaluation of policy options regarding infertility treatments.

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*Address for correspondence: Babak Khoshnood, INSERM U149, 16 Avenue Paul Vaillant Couturier, 94807 VILLEJUIF Cedex, France. E-mail: khoshnood@vjf.inserm.fr*

In this study, we examine time trends in twin and triple births across the regions in France for the period 1972 to 2003, which corresponds to the introduction and widespread diffusion of infertility treatments (Tuppin et al., 1993). We do so using population-based national data and assess regional variations in trends for multiple births separately for same-sex and different-sex twin, as well as, triple births. In order to test and quantify the regional variations in trends for multiple births, we use hierarchical logistic regression models together with a recently proposed measure (median odds ratio) of group-level (e.g., regional) variance in binary outcomes (e.g., twin vs. singleton births).

## Data

We obtained national and regional data on a total number of 23,970,955 singleton, 569,423 twin, and 14,599 triple births from the French National Institute of Statistics and Economic Studies (INSEE). Data on multiple births included all live-births and stillbirths (≥ 28 weeks until 2003, and ≥ 22 weeks for 2003). For gestational ages lower than these limits (28 weeks until 2003 and 22 weeks in 2003), multiple births were registered as such if all were live-births. The number of births was not a multiple of two for twins, or three for triplets, in all regions. This discrepancy may occur even if only one birth in a multiple set is unregistered or is misclassified. Birth data from INSEE are thought to be essentially exhaustive as registration of births is mandatory. The exact percentages of unregistered births, or of errors in registration (e.g., singleton rather than twin), are not known. However, these percentages are likely to be low, and moreover, they are not known to be subject to significant regional variations.

The regions included were all those in the metropolitan France, that is, excluding the region corresponding to French overseas *départements* ('counties'). Data for twin and triple births were available for the periods 1972 to 2003, and 1984 to 2003, respectively. The total number of births varies greatly across regions in France. For example in 2000 to 2003, number of births varied from a high of approximately 700,000 in the Ile-de-France (Parisian) region to a low of about 28,000 in Limousin and 11,000 in Corse; whereas the number of births in most regions was close to the 100,000 to 200,000 range. In order to maintain confidentiality of data for smaller regions, maternal age distribution of births by region were only available for singleton and twin births; moreover, data were aggregated for 3-year periods. Data on maternal age were available for the following four age groups: < 25 years, 25–29 years, 30–34 years and ≥ 35 years. We also obtained data on a total number of 103,515 same-sex, and 48,452 different-sex twin births for the initial (1972–1975) and final (2000–2003) years of the study period.

## Statistical analysis

We estimated the proportion of twin births per 1000 total births (singletons + twins) with corresponding 95% binomial exact confidence intervals (CIs). Proportions of same-sex and different-sex twin births were calculated with the denominators of same-sex twin births + singletons, and different-sex twin births + singletons, respectively. The proportion of triple births was calculated with singletons + twins + triplets as the denominator and reported per 10,000 total births.

For statistical analysis, we estimated two sets of hierarchical logistic regression models for regional trends in multiple births. In the first set, we estimated random-coefficients (random-intercept and random slopes) models to test for regional differences in trends for multiple births, that is, for each outcome (twins, same-sex and different-sex twins, and triplets) we tested the statistical significance of the variance of the random slopes corresponding to time trends in multiple births by region. In particular, we tested whether differences in region-specific trends for twin births remained significant after adjustment for differences in the maternal age distribution.

In the second set, for each outcome, we estimated random-intercept hierarchical logistic regression models at a given time period, for example, 1972 to 1975 or 2000 to 2003. These models allow one to test whether regional differences in multiple births at a given point in time are statistically significant. In addition, using these random-intercept logistic regression models, we calculated a recently proposed measure of group-level heterogeneity for hierarchical logistic regression models, the median odds ratio (MOR; Larsen & Merlo, 2005; Larsen et al., 2000). This measure allows us to quantify regional variations in multiple births at a given time period on the odds ratio scale. It is based on the estimate of the variance of the random effect (intercept) in the two-level logistic regression model and is calculated as follows:

$$\text{Median Odds Ratio (MOR)} = \exp\left[\left(\sqrt{2\times\sigma^2_{u0}}\right)\times\Phi^{-1}(0.75)\right],$$

where $\sigma^2_{u0}$ represents the variance of the random effect (intercept) corresponding to regional differences and $\phi^{-1}$ (0.75) is the inverse of the cumulative distribution (cdf) of the standard normal distribution evaluated at 0.75 (75th percentile).

This measure reflects an 'average' value of the distribution of the overall regional variations in multiple (e.g., twin) births rather than differences corresponding to any two given regions or the range for all possible regional differences. More formally, if one were to estimate all of the odds ratios of twin births across regions with different propensities for twin births, the median odds ratio would represent the median of the distribution of these estimated odds ratios. Thus, the median odds ratio representing regional differences in twin births at a given period of time (e.g., 2000–2003) may be interpreted as follows: a median odds ratio of say 2 would imply that the



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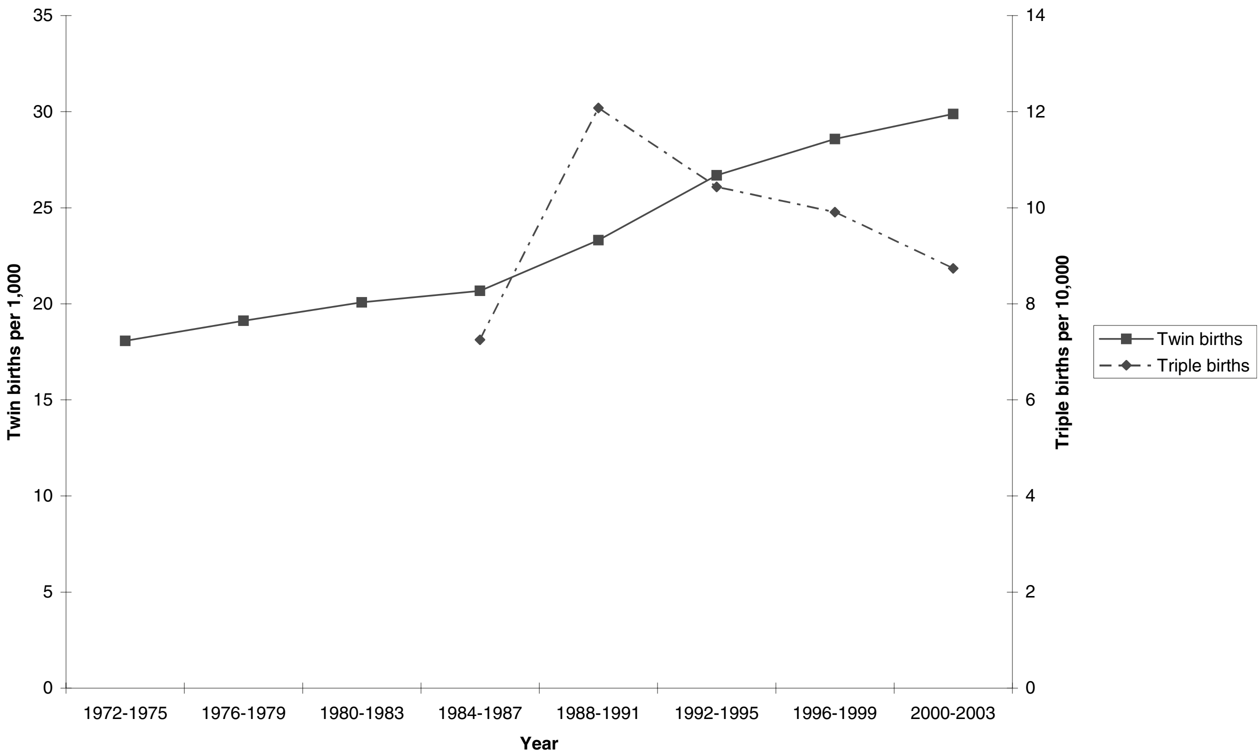


**Figure 1**

Trends in twin and triple births in France; data on twin births were available for the period 1972 – 2003 and for triple births for 1984 – 2003.

odds of a twin birth in a region with higher propensity for twin births as compared with a region with lower propensity for twin births would be equal to or greater than 2 for half of the regions (and lower than 2 for the other half).

## Results

Figure 1 shows the overall trends for twin and triple births in France. Trends for twins are shown for the period 1972 to 2003, and for triple births in 1984 to 2003 based on the available data for our study. The proportion of twin births consistently increased from 18.1 per 1000 in 1972 to 1975 to 29.9 per 1000 in 2000 to 2003. In contrast, the proportion of triple births increased from 7.3 per 10,000 in 1984 to 1987 to 12.1 per 10,000 in 1988 to 1991 and subsequently decreased to 8.7 per 10,000 in 2000 to 2003.

Table 1 shows the proportion of twin births across regions in France for the two periods 1972 to 1975 and 2000 to 2003 (detailed results for other periods available from authors). There were significant regional differences in the proportion of twin births in both periods ($p < .001$). Moreover, while twin births increased for all regions, the rates of increase varied significantly among them (see Table 2). Overall the odds of a twin birth increased by about 70% (odds ratio [OR] 1.67, 95% CI 1.66–1.69) in France between 1972 and 1975, and 2000 and 2003. The maternal age-adjusted odds ratio was 1.44 (95% CI 1.42–1.45), that is, about one-third lower than the unadjusted odds ratio. The greatest rate of increase occurred in the region of Ile-de-France, which includes Paris and its surrounding communities where the maternal age-adjusted odds of a twin birth increased by about 50% (age-adjusted OR 1.51; 95% CI 1.48–1.55). The lowest rate of increase occurred in Nord-Pas-de-Calais, where the maternal age-adjusted odds of a twin birth increased by 25% (age-adjusted OR, 1.25; 95% CI 1.21–1.30).

Estimates from a random-coefficient hierarchical logistic regression model of trends in twin births showed that the differences in trends for twin births across regions were statistically significant ($p$ values for random slopes corresponding to time trends $< .001$). In addition, median odds ratios obtained from period-specific random-effects logistic regression models of twin births suggested relatively small but increasing regional variations in maternal age-adjusted twin births over time; the median odds ratios were 1.04 and 1.07 in 1972 to 1975, and 2000 to 2003, respectively. These median odds ratios may be interpreted as follows: in 1972 to 1975, maternal age-adjusted odds ratio of a twin birth in two regions with different rates of twin births were equal to or greater than 1.04 (i.e., increased by a factor of 4% or

**Table 1**

Region-Specific Proportions of Twin Births in France, 1972–1975 and 2000–2003

| | 1972–1975 | | | | 2000–2003 | | | |
|---|---|---|---|---|---|---|---|---|
| Region | *N*[*] | Twins per 1000 births[*] | 95 % CI[†] | *p*[#] | *N*[*] | Twins per 1000 births[*] | 95 % CI[†] | *p*[#] |
| Ile-de-France | 645,907 | 18.4 | 18.0–18.7 | < .001 | 698,656 | 32.3 | 31.9–32.7 | < .001 |
| Champagne-Ardenne | 92,517 | 18.7 | 17.8–19.6 | | 66,796 | 30.3 | 29.0–31.6 | |
| Picardie | 117,247 | 17.6 | 16.9–18.4 | | 101,196 | 27.9 | 26.9–29.0 | |
| Haute-Normandie | 110,427 | 18.2 | 17.5–19.1 | | 94,167 | 29.8 | 28.8–30.9 | |
| Centre | 132,267 | 16.3 | 15.6–17.0 | | 119,433 | 27.4 | 26.4–28.3 | |
| Basse-Normandie | 88,176 | 17.3 | 16.5–18.2 | | 70,068 | 28.9 | 27.7–30.2 | |
| Bourgogne | 94,893 | 17.7 | 16.9–18.6 | | 72,214 | 30.4 | 29.1–31.6 | |
| Nord-Pas-de-Calais | 291,124 | 19.7 | 19.2–20.2 | | 227,226 | 27.7 | 27.0–28.4 | |
| Lorraine | 148,066 | 18.5 | 17.9–19.2 | | 110,227 | 30.9 | 29.9–32.0 | |
| Alsace | 94,371 | 17.9 | 17.1–18.6 | | 89,784 | 30.4 | 29.3–31.6 | |
| Franche-Comté | 71,882 | 17.2 | 16.3–18.2 | | 56,961 | 29.4 | 28.0–30.8 | |
| Pays de la Loire | 197,908 | 17.6 | 17.0–18.2 | | 174,637 | 28.2 | 27.4–29.0 | |
| Bretagne | 167,137 | 18.8 | 18.1–19.5 | | 145,972 | 29.4 | 28.5–30.3 | |
| Poitou-Charentes | 91,938 | 16.5 | 15.6–17.3 | | 72,884 | 25.7 | 24.5–26.8 | |
| Aquitaine | 139,930 | 17.1 | 16.4–17.8 | | 131,094 | 29.2 | 28.3–30.1 | |
| Midi-Pyrénées | 116,598 | 17.6 | 16.9–18.4 | | 117,646 | 27.7 | 26.8–28.7 | |
| Limousin | 34,961 | 17.1 | 15.7–18.5 | | 27,593 | 27.0 | 25.2–29.0 | |
| Rhône-Alpes | 302,334 | 18.2 | 17.7–18.7 | | 305,844 | 30.3 | 29.7–30.9 | |
| Auvergne | 75,722 | 17.0 | 16.1–17.9 | | 55,472 | 28.4 | 27.1–29.8 | |
| Languedoc-Roussillon | 88,529 | 18.0 | 17.2–18.9 | | 109,415 | 30.8 | 29.8–31.8 | |
| Provence-Alpes-Côte d'Azur | 188,122 | 18.3 | 17.7–18.9 | | 221,712 | 30.4 | 29.7–31.1 | |
| Corse | 11,077 | 20.6 | 18.1–23.5 | | 11,093 | 31.0 | 27.9–34.4 | |
| All | 3,301,063 | 18.1 | 17.9–18.2 | | 3,080,090 | 29.9 | 29.7–30.1 | |

Note: [*]Total number of singleton + twin births.

[†]95% binomial exact confidence intervals.

[#]$\chi^2$ test for regional differences in each period.

more) for half of the regions. By 2000 to 2003, regional differences in age-adjusted odds of a twin birth were 7% or more for half of the regions.

Table 3 shows trends in same-sex and different-sex twin births across the regions in France. Overall, the proportion of same-sex twin births increased from 12.9 per 1000 (95% CI 12.8 – 13.1) births (singletons + same-sex twin births) in 1972 to 1975 to 20.0 (95% CI 19.9–20.2) in 2000 to 2003, equivalent to a 56% increase in the odds of a same-sex twin birth between the two periods (OR 1.56; 95% CI 1.54–1.58). The proportion of different-sex twin births increased from 5.4 (95% CI 5.3–5.4) per 1000 to 10.3 (95% CI 10.2–10.4) per 1000 corresponding to a 93% increase in the odds of a different-sex twin birth between the two periods (OR 1.93; 95% CI 1.89–1.96). Hence, in relative terms (odds ratios), the increase in different-sex twin births was substantially greater than that of same-sex twin births.

Trends in same-sex, and more so, different-sex twin births varied significantly across regions; variance estimates for the random component of the slopes (time trends) in hierarchical logistic regression models for both same-sex and different-sex twin births were statistically significant ($p < .001$). However, in general, trends for same-sex and different-sex twin births were not consistent across regions, that is, regions with highest rates of increase in same-sex twin births were not necessarily the ones with the highest rates of increase for different-sex twin births and vice-versa. For example, Languedoc-Roussillon had a lower than average increase in same-sex twin births but the highest rate of increase in different-sex twin births. In general, regions with the highest rates of increase in different-sex twin births were also the ones with the highest rates of increase in maternal age-adjusted odds of twin births; this was less the case for same-sex twin births.

Median odds ratio estimates suggested a difference of 4% or more in the odds of a same-sex twin birth (MOR 1.04) in 2000 to 2003 and a difference of 9% or more (MOR 1.09) in the odds of a different-sex twin birth for half of the regions in France. These estimates suggest that regional variations in different-sex twin births were more than two-fold greater than the variations in same-sex twin births.

Table 4 shows proportions of triple births in 1984 to 1987 and 2000 to 2003, as well as the ratio of triple to twin births for each region. There were statistically significant differences in the region-specific proportions of triple births in both periods ($p < .001$). The triple/twin ratios decreased for essentially all regions, but more so for certain regions (e.g., Basse-Normandie), which had higher triple/twin ratios to begin with. There remained substantial regional differences in triple/twin ratios in the most recent period. The ratio in Languedoc-Roussillon, the region with the highest ratio, was almost two-fold higher than that of Haute-Normandie, the region with the lowest ratio.

Table 5 shows trends in the region-specific odds of a triple birth for the entire period from 1984 to 2003. Trends in triple births varied considerably across regions ($p$ values < .001 for variance of random slopes corresponding to time trends). However, for most regions, the odds of a triple birth increased between 1984 and 1987, and 1988 and 1991, and decreased thereafter. In addition, period-specific median odds ratio estimates suggested a decrease in regional variations for triple births since the early 1990s; the median odds ratio estimate was 1.33 in 1988 to 1991 as compared with 1.17 in 2000 to 2003. Hence, in contrast to twin births, regional variations in triple births had a tendency to decrease over time.

## Discussion

In summary, our results show consistent increases in twin, but not triple births, over time. Overall, the odds of a twin birth increased by about 70% between 1972 and 1975, and 2000 and 2003 in France. After adjustment for maternal age, the increase in the odds of a twin birth was approximately 44%, that is, about one third lower than the unadjusted estimate. Trends for both twin and triple births varied significantly across regions. Moreover, maternal age-adjusted median odds ratio estimates based on hierarchical logistic regression models suggested relatively small but increasing regional variations in twin births over time. The odds of a different-sex twin birth increased substantially more than that of a same-sex twin birth and regional variations in different-sex twin births were more than two-fold greater than the variations in same-sex twin births. In contrast with these trends for twin births, both the overall probability of, and the

**Table 2**

Region-Specific Trends in the Odds of a Twin Birth in 2000–2003 as Compared with 1972–1975

| Region | Odds Ratio (OR)* | 95 % CI† | $p$# | Maternal age-adjusted OR* | 95 % CI† | $p$# |
|---|---|---|---|---|---|---|
| Ile-de-France | 1.78 | 1.74–1.82 | < .001 | 1.51 | 1.48–1.55 | < .001 |
| Champagne-Ardenne | 1.64 | 1.54–1.75 | | 1.40 | 1.31–1.50 | |
| Picardie | 1.60 | 1.51–1.70 | | 1.38 | 1.30–1.46 | |
| Haute-Normandie | 1.65 | 1.56–1.75 | | 1.42 | 1.34–1.51 | |
| Centre | 1.70 | 1.61–1.80 | | 1.46 | 1.38–1.55 | |
| Basse-Normandie | 1.69 | 1.58–1.80 | | 1.47 | 1.37–1.57 | |
| Bourgogne | 1.74 | 1.63–1.85 | | 1.50 | 1.41–1.60 | |
| Nord-Pas-de-Calais | 1.42 | 1.37–1.47 | | 1.25 | 1.21–1.30 | |
| Lorraine | 1.69 | 1.61–1.78 | | 1.47 | 1.40–1.55 | |
| Alsace | 1.72 | 1.62–1.83 | | 1.47 | 1.38–1.57 | |
| Franche-Comté | 1.73 | 1.60–1.86 | | 1.49 | 1.38–1.61 | |
| Pays de la Loire | 1.62 | 1.55–1.69 | | 1.40 | 1.33–1.46 | |
| Bretagne | 1.58 | 1.51–1.66 | | 1.34 | 1.28–1.41 | |
| Poitou-Charentes | 1.57 | 1.47–1.69 | | 1.37 | 1.27–1.47 | |
| Aquitaine | 1.73 | 1.64–1.82 | | 1.50 | 1.42–1.58 | |
| Midi-Pyrénées | 1.59 | 1.50–1.68 | | 1.36 | 1.28–1.44 | |
| Limousin | 1.60 | 1.43–1.78 | | 1.34 | 1.20–1.50 | |
| Rhône-Alpes | 1.69 | 1.63–1.75 | | 1.47 | 1.42–1.52 | |
| Auvergne | 1.69 | 1.57–1.82 | | 1.47 | 1.36–1.58 | |
| Languedoc-Roussillon | 1.73 | 1.63–1.84 | | 1.50 | 1.41–1.60 | |
| Provence-Alpes-Côte d'Azur | 1.68 | 1.61–1.75 | | 1.46 | 1.40–1.52 | |
| Corse | 1.52 | 1.28–1.80 | | 1.32 | 1.11–1.57 | |
| All | 1.67 | 1.66–1.69 | | 1.44 | 1.42–1.45 | |

Note: *Reference period: 1972–1975
†95% confidence intervals
#Test for statistical significance of differences in trends across regions; i.e., significance of the random component of the slope for time trends across regions in hierarchical logistic regression models.



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**Table 3**

Region-Specific Trends in the Odds of Same-Sex and Different-Sex Twin Births in 2000–2003 as Compared with 1972–1975

| | Same-sex twin births | | | Different-sex twin births | | |
|---|---|---|---|---|---|---|
| Region | Odds Ratio* | 95 % CI† | p# | Odds Ratio* | 95 % CI† | p# |
| Ile-de-France | 1.61 | 1.57–1.66 | < .001 | 2.21 | 1.73–2.30 | < .001 |
| Champagne-Ardenne | 1.52 | 1.40–1.64 | | 1.95 | 1.73–2.19 | |
| Picardie | 1.56 | 1.46–1.68 | | 1.68 | 1.52–1.86 | |
| Haute-Normandie | 1.54 | 1.43–1.65 | | 1.96 | 1.76–2.17 | |
| Centre | 1.62 | 1.52–1.73 | | 1.90 | 1.72–2.10 | |
| Basse-Normandie | 1.60 | 1.48–1.74 | | 1.87 | 1.66–2.10 | |
| Bourgogne | 1.64 | 1.52–1.77 | | 1.96 | 1.75–2.21 | |
| Nord-Pas-de-Calais | 1.43 | 1.37–1.50 | | 1.39 | 1.30–1.48 | |
| Lorraine | 1.49 | 1.41–1.59 | | 1.83 | 1.68–2.00 | |
| Alsace | 1.67 | 1.55–1.79 | | 1.83 | 1.64–2.05 | |
| Franche-Comté | 1.62 | 1.48–1.77 | | 1.97 | 1.73–2.25 | |
| Pays de la Loire | 1.48 | 1.40–1.56 | | 2.00 | 1.85–2.17 | |
| Bretagne | 1.50 | 1.41–1.58 | | 1.77 | 1.63–1.92 | |
| Poitou-Charentes | 1.46 | 1.34–1.58 | | 1.91 | 1.67–2.18 | |
| Aquitaine | 1.66 | 1.56–1.76 | | 1.89 | 1.72–2.07 | |
| Midi-Pyrénées | 1.43 | 1.34–1.53 | | 2.04 | 1.84–2.26 | |
| Limousin | 1.57 | 1.38–1.79 | | 1.66 | 1.36–2.02 | |
| Rhône-Alpes | 1.59 | 1.53–1.66 | | 1.90 | 1.79–2.02 | |
| Auvergne | 1.57 | 1.44–1.72 | | 1.97 | 1.73–2.24 | |
| Languedoc-Roussillon | 1.50 | 1.40–1.62 | | 2.33 | 2.09–2.60 | |
| Provence-Alpes-Côte d'Azur | 1.55 | 1.48–1.63 | | 1.96 | 1.82–2.12 | |
| Corse | 1.62 | 1.33–1.98 | | 1.28 | 0.93–1.75 | |
| All | 1.56 | 1.54–1.58 | | 1.93 | 1.89–1.96 | |

Note: *Reference period: 1972–1975.
†95% confidence intervals.
#Test for statistical significance of differences in trends across regions; i.e., significance of the random component of the slope for time trends across regions in hierarchical logistic regression models.

regional variations in, triple births have been decreasing since the early 1990s.

In our study, we made use of the median odds ratio, a recently proposed measure of group-level variation in a binary outcome based on variance estimates from hierarchical logistic regression models. To our knowledge, this measure has not been previously used in studies related to perinatal outcomes. The median odds ratio allows in particular an assessment of group-level variance after adjustment for individual-level (compositional) differences across groups (e.g., regions) on an odds ratio scale familiar to epidemiologists. In addition, as our analysis shows, an assessment of changes in median odds ratio over time provides information about temporal trends in group-level variations for a binary outcome. Specifically, the measure allowed us to both quantify regional variations in multiple births and conclude that variations in twin births increased whereas those related to triple births decreased over time.

Since the median odds ratio measures 'average' variations over all regions, identification of extreme cases, which may also be useful in evaluation studies, requires an additional examination of outcomes for each region. Specific identification of regions with particularly high or low rates of multiple births would be possible using a fixed-effects modeling approach, which allows estimation of the odds of say a twin birth for one region as compared with a 'reference' region. However, the fixed-effects approach is not practical when the number of regions is (relatively) large and/or if the number of births for at least some of the regions is small, particularly for rare outcomes such as triple or higher order births. In addition, examination of differences in trends for multiple births across regions would often not be practical using a fixed-effects modeling approach as the number of interaction effects (between regions and time periods) that need to be included in the models are large and not always estimable. Hence, the random-slope modeling approach we have used is usually more suitable for examining variations in trends across regions.

The regional differences in multiple births we documented in our study were comparable to country-level differences observed across several western and northern European countries in recent periods (Kaprio & Marttila, 2005; Macfarlane & Blondel, 2005). This in turn suggests that country-level comparisons of

**Table 4**

Region-Specific Proportions of Triple Births and Triplet/Twin Ratios in 1984–1987 and 2000–2003

| | 1984–1987 | | | 2000–2003 | | |
|---|---|---|---|---|---|---|
| Region | Triples per 10,000 births* | 95 % CI† | Triplet/twin ratio# | Triples per 10,000 births* | 95 % CI† | Triplet/twin ratio# |
| Ile-de-France | 8.1 | 7.4–8.8 | 4.4 | 9.6 | 8.9–10.3 | 3.0 |
| Champagne-Ardenne | 9.3 | 7.3–11.7 | 5.0 | 9.0 | 6.8–11.6 | 3.0 |
| Picardie | 5.2 | 3.9–6.8 | 3.0 | 9.2 | 7.4–11.2 | 3.3 |
| Haute-Normandie | 4.3 | 3.1–5.7 | 2.4 | 5.4 | 4.0–7.1 | 1.8 |
| Centre | 8.0 | 6.5–9.8 | 4.9 | 7.0 | 5.6–8.7 | 2.6 |
| Basse-Normandie | 9.6 | 7.6–12.1 | 5.5 | 6.1 | 4.4–8.3 | 2.1 |
| Bourgogne | 9.9 | 7.9–12.3 | 5.6 | 10.0 | 7.8–12.5 | 3.3 |
| Nord-Pas-de-Calais | 4.8 | 4.0–5.8 | 2.4 | 8.9 | 7.7–10.2 | 3.2 |
| Lorraine | 8.9 | 7.3–10.6 | 4.8 | 6.8 | 5.3–8.5 | 2.2 |
| Alsace | 7.6 | 5.9–9.6 | 4.2 | 7.8 | 6.1–9.8 | 2.6 |
| Franche-Comté | 7.6 | 5.6–10.2 | 4.4 | 10.0 | 7.6–13.0 | 3.4 |
| Pays de la Loire | 9.2 | 7.9–10.8 | 5.2 | 9.5 | 8.1–11.1 | 3.4 |
| Bretagne | 6.9 | 5.6–8.3 | 3.7 | 8.5 | 7.1–10.1 | 2.9 |
| Poitou-Charentes | 8.5 | 6.5–10.8 | 5.2 | 7.8 | 5.9–10.1 | 3.0 |
| Aquitaine | 4.0 | 3.0–5.3 | 2.3 | 8.0 | 6.5–9.7 | 2.7 |
| Midi-Pyrénées | 4.2 | 3.1–5.7 | 2.4 | 5.4 | 4.1–6.8 | 1.9 |
| Limousin | 6.6 | 4.0–10.4 | 3.9 | 5.4 | 3.0–9.0 | 2.0 |
| Rhône-Alpes | 5.8 | 5.0–6.8 | 3.2 | 10.2 | 9.1–11.4 | 3.4 |
| Auvergne | 7.0 | 5.1–9.5 | 4.1 | 8.6 | 6.4–11.5 | 3.0 |
| Languedoc-Roussillon | 8.9 | 7.1–11.0 | 4.9 | 10.7 | 8.9–12.9 | 3.5 |
| Provence-Alpes-Côte d'Azur | 8.5 | 7.3–9.9 | 4.6 | 8.8 | 7.6–10.2 | 2.9 |
| Corse | 10.3 | 5.3–18.0 | 5.0 | 10.8 | 5.6–18.9 | 3.5 |
| All | 7.3 | 7.0–7.6 | 4.0 | 8.7 | 8.4–9.1 | 2.9 |

Note: *Total number of singleton + twin + triple births; $\chi^2$ test for overall regional differences in each period ($p < .001$).
†95% binomial exact confidence intervals.
#Triple/Twin birth ratios by region (x 100).

multiple birth rates may neglect important within-country heterogeneities.

Regions constitute a 'natural' unit of analysis for studying health system characteristics and outcomes in France. This is particularly the case for multiple births as national policies regulating infertility treatments include needs assessment for in vitro fertilization at the regional level. A national committee oversees the process and regulates the supply and quality of services. The observed trends for increasing regional variations in twin births imply that regional differences in the risks and the healthcare burden related to twin births may increase over time. In contrast, it appears that changes in practice patterns, in particular those limiting the transfers of three embryos or more (Andersen et al., 2005; Roalier et al., 1993), have resulted in both a decrease in the overall probability of triple births, as well as lesser regional variations. Nevertheless, the timing and pace of the decrease in triple births varied considerably across regions. In particular, certain regions (Nord-Pas-de-Calais, Rhône-Alpes) had persistently higher odds of triple births over time.

The observed trends and regional variations in multiple births have several potential explanations other than those related to infertility treatments. The frequency of dizygotic twinning varies considerably worldwide, whereas that of spontaneous monozygotic twinning tends to be fairly constant. Dizygotic twinning is associated with several risk factors (Allen, 1984; Hankins & Saade, 2005) including maternal age, parity, ethnic origin, genetic factors, and nutritional factors. In addition, studies that predate the introduction of infertility treatments (Allen, 1984; Daguet, 2002; Hemon et al., 1981; Pison & D'Addato, 2006) have found both short-term (including seasonal) and long-term temporal trends in twin births.

Pison and D'Addato (2006) discussed these trends for several European countries. While the baseline twinning rates and the trends prior to 1970s differ across countries, for all countries there were decreasing trends in twin births between 1950s and mid-1970s, with increases thereafter. The decline in twinning rates observed between 1950s and 1970s may be explained in part by a younger maternal age distribution and lower levels of parity, and consequently a decrease in

**Table 5**

Region-Specific Trends in the Odds of a Triple Birth, 1984–2003

| | 1988–1991 | | | 1992–1995 | | | 1996–1999 | | | 2000–2003 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Region | OR* | 95% CI† | $p^{\#}$ | OR* | 95% CI† | $p^{\#}$ | OR* | 95% CI† | $p^{\#}$ | OR* | 95% CI† | $p^{\#}$ |
| Ile-de-France | 1.5 | 1.3–1.7 | < .001 | 1.4 | 1.2–1.5 | < .001 | 1.2 | 1.1–1.4 | < .001 | 1.2 | 1.1–1.3 | < .001 |
| Champagne-Ardenne | 1.1 | 0.8–1.5 | | 1.1 | 0.8–1.6 | | 1.6 | 1.2–2.2 | | 1.0 | 0.7–1.4 | |
| Picardie | 2.5 | 1.9–3.4 | | 1.8 | 1.3–2.5 | | 1.9 | 1.4–2.7 | | 1.8 | 1.3–2.4 | |
| Haute-Normandie | 2.4 | 1.7–3.4 | | 2.4 | 1.7–3.4 | | 1.9 | 1.3–2.8 | | 1.3 | 0.8–1.9 | |
| Centre | 1.8 | 1.4–2.3 | | 0.9 | 0.7–1.3 | | 1.2 | 0.9–1.5 | | 0.9 | 0.7–1.2 | |
| Basse-Normandie | 0.9 | 0.7–1.3 | | 0.6 | 0.4–0.9 | | 0.3 | 0.2–0.5 | | 0.6 | 0.4–0.9 | |
| Bourgogne | 0.7 | 0.5–1.0 | | 1.2 | 0.9–1.7 | | 1.5 | 1.1–2.0 | | 1.0 | 0.7–1.4 | |
| Nord-Pas-de-Calais | 2.0 | 1.6–2.5 | | 1.7 | 1.3–2.1 | | 1.8 | 1.5–2.3 | | 1.8 | 1.5–2.3 | |
| Lorraine | 1.6 | 1.2–2.0 | | 1.1 | 0.9–1.5 | | 1.3 | 1.0–1.7 | | 0.8 | 0.6–1.0 | |
| Alsace | 1.3 | 0.9–1.8 | | 1.2 | 0.8–1.6 | | 1.1 | 0.8–1.5 | | 1.0 | 0.7–1.4 | |
| Franche-Comté | 2.2 | 1.5–3.1 | | 2.0 | 1.4–2.9 | | 1.6 | 1.1–2.3 | | 1.3 | 0.9–1.9 | |
| Pays de la Loire | 1.3 | 1.1–1.6 | | 1.2 | 1.0–1.5 | | 0.9 | 0.7–1.1 | | 1.0 | 0.8–1.3 | |
| Bretagne | 1.8 | 1.4–2.3 | | 1.0 | 0.8–1.3 | | 1.2 | 0.9–1.6 | | 1.2 | 1.0–1.6 | |
| Poitou-Charentes | 1.0 | 0.7–1.4 | | 1.2 | 0.9–1.7 | | 1.0 | 0.7–1.4 | | 0.9 | 0.6–1.3 | |
| Aquitaine | 1.9 | 1.4–2.7 | | 2.4 | 1.7–3.3 | | 1.8 | 1.3–2.6 | | 2.0 | 1.4–2.8 | |
| Midi-Pyrénées | 2.3 | 1.6–3.2 | | 2.1 | 1.5–3.0 | | 2.3 | 1.6–3.2 | | 1.3 | 0.9–1.9 | |
| Limousin | 1.7 | 0.9–3.0 | | 3.1 | 1.8–5.3 | | 0.9 | 0.4–1.7 | | 0.8 | 0.4–1.6 | |
| Rhône-Alpes | 2.0 | 1.7–2.5 | | 2.0 | 1.6–2.4 | | 1.9 | 1.6–2.3 | | 1.7 | 1.5–2.1 | |
| Auvergne | 2.2 | 1.6–3.2 | | 1.7 | 1.2–2.5 | | 1.7 | 1.1–2.5 | | 1.2 | 0.8–1.9 | |
| Languedoc-Roussillon | 1.6 | 1.3–2.1 | | 1.1 | 0.8–1.5 | | 1.1 | 0.8–1.5 | | 1.2 | 0.9–1.6 | |
| Provence-Alpes-Côte d'Azur | 2.1 | 1.8–2.5 | | 1.6 | 1.3–2.0 | | 1.5 | 1.2–1.8 | | 1.0 | 0.8–1.3 | |
| Corse | 3.2 | 1.7–6.0 | | 0.5 | 0.2–1.4 | | 0.8 | 0.3–1.9 | | 1.0 | 0.5–2.3 | |
| All | 1.7 | 1.6–1.8 | | 1.4 | 1.4–1.5 | | 1.4 | 1.3–1.4 | | 1.2 | 1.1–1.3 | |

Note: *Odds of a triple birth in the given period as compared with the reference period 1984–1987.
†95% confidence intervals; due to rounding some limits of confidence intervals overlap with point estimates.
#Test for statistical significance of differences in trends across regions; i.e., significance of the random component of the slope for time trends across regions in hierarchical logistic regression models.

dizygotic twin births. In addition, it has been hypothesized (Hemon et al., 1981; Pison & D'Addato, 2006) that a 'demographic selection' mechanism, that is, the declining fertility of women, particularly highly fecund, twin-prone women, may explain the decline in dizygotic twinning rates.

Regional differences have also been reported in several countries, including France, prior to the introduction of infertility treatments (Allen, 1984, 1988; Fellman & Eriksson, 2005; Hemon et al., 1981). In a study of trends in dizygotic twinning rates in France between 1901 and 1968, Hemon and colleagues (Hemon et al., 1981) found geographic heterogeneities in the declining trends for dizygotic twinning rates across 90 administratively defined districts. Geographic variations in the secular rates of dizygotic twinning were correlated with birth rates but not other characteristics, which were meant to measure 'breaking of genetic isolation' due to migration, resulting in a decline in the proportion of women that are homozygotes for the genes favoring dizygotic twinning. The authors concluded that the demographic selection mechanism (decline in the fertility of highly fecund, twin-prone women) was a plausible explanation for the declining trends in dizygotic twinning rates.

Other factors, including environmental ones (Hemon et al., 1981), may have also contributed to these trends and, in general, the underlying mechanisms for trends in multiple births prior to the introduction of fertility treatments are not entirely understood. It is possible that the effects of certain factors that influenced the trends in multiple births prior to the introduction of infertility treatments have persisted in the more recent periods. If so, the impact of such factors on the trends documented in our study is not clear.

Nonetheless, the regional differences in trends for multiple births observed in our study are likely to reflect, at least in part, differences in access to, as well as, variations in practice patterns for assisted reproductive technologies. This explanation is consistent with the observed higher rates of increase, and the greater regional differences in the trends for different-sex as compared with same-sex twin births. While monozygotic twinning does increase with assisted reproductive technologies, the majority of pregnancies following ovarian stimulation and in vitro fertilization techniques are from separate ova and therefore dizygotic (Hankins & Saade, 2005). Therefore, the greater rate of increase in different-sex twin births is likely to be explained by the increase in infertility treatments since all different-sex (as well as a proportion of same-sex) twin births are dizygotic.

In our study, we found substantial variations in the trends for twin versus triple births across regions. As a result, in the most recent period, the triple/twin ratio was almost two-fold higher in regions with a high triple/twin ratio (e.g., Languedoc-Roussillon and Pays de Loire) as compared with those with a low triple/twin ratio (e.g., Haute-Normandie and Midi-Pyrénées). The reasons for these differences require further analysis but they are most likely, at least in part, due to regional differences in the supply of, and/or practice patterns for, infertility treatments. This explanation is consistent with the observed differences in the rates for twin and triple births across the countries in Europe. Countries such as Denmark, Finland and Sweden that have a high availability (supply) of in vitro fertilization, along with conservative practices aimed at reducing the number of fetuses (e.g., by limiting transfers of three or more embryos; Andersen et al., 2005), tend to have lower triple to twin birth ratios (Kaprio & Marttila, 2005; Macfarlane & Blondel, 2005). This results from the (relatively) greater increases in twin as compared with triple (and higher order) births in these countries. On the other hand, countries such as Germany and the United Kingdom that have an overall lower supply of infertility treatments but less conservative practice patterns (Andersen et al., 2005; e.g., practices primarily aimed at increasing the pregnancy rate with a higher number of embryo transfers), tend to have higher triple to twin birth ratios (Macfarlane & Blondel, 2005).

Multiple births are at higher risks for several obstetric, neonatal and childhood complications (Papiernik, 2005; Pharoah, 2005; Shinwell & Nahum, 2005; Skupski, 2005), including notably a five- to ten-fold higher risk of very preterm birth (< 32 weeks) and cerebral palsy. Substantial costs are also associated with multiple pregnancies (Hall & Callahan, 2005), including those related to maternal and neonatal care, and additional long-term family and societal costs of neonatal disabilities and handicaps. Both the risks and the costs of multiple births are much higher in case of triple, as compared with twin births. Our results suggest that the population-level impact of risks associated with twin births increased over time, and more so for some regions than others. As a result, twin births had a greater impact on outcomes and healthcare needs for certain regions (e.g., Ile-de-France). On the other hand, our findings imply that overall regional differences in triplets and their attendant risks and costs decreased over time.

Several limitations and caveats should be considered in the interpretation of our results. Due to confidentiality considerations, other than maternal age, we had no other individual-level data to account for compositional differences across regions. As dizygotic twinning is associated with several risk factors other than maternal age, our interpretations of the observed trends and regional differences in maternal age-adjusted twin births must remain tentative. However, we are not aware of any evidence suggesting that there have been significant temporal changes in the distributions of known risk factors (other than maternal age) for multiple births across regions. Therefore, it is likely that regional differences in the supply and/or practice patterns in assisted reproductive technologies can account for much of the observed differences in the trends for multiple births across regions.

## Conclusion

Along with the increasing use of infertility treatments, the proportion of twin births consistently increased across all regions in France. On the other hand, triple births increased until the early 1990s but decreased thereafter. These trends varied significantly across regions, and the observed regional variations were comparable to country-level differences documented across several western and northern European countries in recent periods. Our results suggest that regional disparities in the risks and the healthcare burden related to twin, but not triple, births increased over time. Regional differences in multiple births need to be monitored and used to inform policies aimed at regulating the use of infertility treatments.

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