



**Special Report: Prevalence of Neural Tube Defects in younger
mothers in Europe 2000-2008: Analysis of the EUROCAT
database**

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WHO Collaborating Centre for the Surveillance of Congenital Anomalies

Prevalence of Neural Tube Defects in younger mothers in Europe 2000-2008: Analysis of the EUROCAT database

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Background

In Europe, the prevalence of neural tube defects (NTD) excluding chromosomal anomalies is 9.43 per 10,000 births, 2000-2008, and accounts for approximately 5% of all congenital anomalies¹. Teenage mothers have a significantly greater risk of NTD compared to older mothers, particularly anencephaly². One explanation is that teenage mothers are less likely to take periconceptional folic acid or have poorer nutrition. However, it is not clear why this would not apply to their risk of spina bifida. Previous studies have not analysed specific risks in the younger teenage mothers <20 years of age.

Aims of study:

1. To investigate the risk of NTD in younger teenage mothers (<15 years, 15 years, 16 years, 17 years, 18 years, 19 years) compared to mothers aged 25-29 years (baseline).
2. To update the risk estimate in Loane et al² for NTD in mothers <20 years, with more years of data (adding 2005-2008 to 2000-2004) compared to mothers aged 25-29 years.

Methodology

EUROCAT (European Surveillance of Congenital Anomalies) is a network of population-based registries established in 1979 to conduct epidemiologic surveillance of congenital anomalies in Europe. It currently has over 40 member registries in 20 countries covering a quarter of all births in EU³. Information on each of the member registries and their methods of case ascertainment are available on the EUROCAT website⁴. The EUROCAT Central Registry database consists of all cases of congenital anomalies notified by regional or national registries including live born cases (LB), cases resulting in fetal deaths from twenty weeks gestational age (FD) and cases that were subsequently terminated following prenatal diagnosis of a congenital anomaly (TOPFA). The EUROCAT database is not a static database as registries receive case notifications on an ongoing basis from

a variety of local sources and once verified the additional cases are included in the next data transmission to EUROCAT.

Registries with data on maternal age for at least 80% of all births in the population covered by the registry were included in the study. The final study population consisted of 25 registries in 15 European countries. Two countries (Croatia and Poland) were unable to provide the number of births to mothers <20 years by single year of age (<=15, 16, 17, 18 and 19 years) hence they were only included in the analysis using the 5 standard maternal age groups (<20, 20-24, 25-29, 30-34 and 35+ years). Maternal age was recorded for 98.99% of the birth population 2000-2008, although this varied by registry from 83%-100%.

Cases of neural tube defects (NTD) identified by the following ICD9 /ICD10 codes: 740, 741, 7420, Q00, Q01 and Q05 were extracted from the central database 2000-2008. NTD cases were classified into three mutually exclusive groups: anencephaly, spina bifida (without anencephaly or encephalocele), and encephalocele (without anencephaly). NTD cases with chromosomal anomalies were excluded from the study.

Maternal Age Corrections

Since many NTD result in TOPFA, there was a potential bias in the data measuring maternal age among NTD cases compared to maternal age of non-NTD births occurring in the population. Therefore maternal age corrections were applied to mothers of all TOPFA cases by assuming that cases would have survived to term (40 weeks) if a termination had not taken place. The child's expected date of delivery (EDD) was calculated by adding the number of weeks from TOPFA to delivery at 40 weeks to get the EDD. For instance, the EDD of a case terminated at 15 weeks on the 1st January 2001 would be 25th June 2001, assuming 40 weeks GA. Maternal age of the TOPFA case was then corrected to maternal age at the EDD, rather than maternal age at TOPFA.

Maternal age correction factors were applied to 882 mothers of TOPFA cases in the teenage mother analysis and 2,759

mothers of TOPFA cases in the standard maternal age analysis. GA, full DOB of TOPFA case and full maternal DOB information were available for 89.0% of TOPFA cases in the teenage mother analysis. Antwerp, Mainz & Saxony-Anhalt provide maternal year of birth only, thus maternal age corrections use 30th June as substitute day and month of birth for these registries. In addition, Saxony-Anhalt only provides month and year of birth for each case so correction calculations substitute unknown day of birth with the 15th of each month of birth. EDD for these 3 registries accounted for 7.9% of TOPFA cases. Actual maternal age at TOPFA was used in 27 cases (3.1%) as no GA info was available for 10 cases and maternal DOB (day, month or year) was unavailable for a further 17 cases. Maternal age was uncorrected for 129 (4.7%) of TOPFA cases in the standard maternal age analysis, where the actual maternal age at TOPFA was used.

Statistical Analysis

Total prevalence rates per 10,000 births were calculated within each maternal age group as:

the number of cases among LB + FD + TOPFA for specific age group/ total number of livebirths + stillbirths in the population for specific age group* 10,000.

The maternal age analysis consisted of 2 component parts:

1. analysis of NTD risk in teenage mothers compared to the baseline maternal age group (mothers aged 25-29 years)
2. analysis of maternal age specific risks in mothers <20, 20-24, 30-34 and 35+ years mothers compared to the baseline maternal age group (mothers aged 25-29 years).

Maternal age was entered as a categorical variable (4 maternal age groups: <18, 18, 19, 25-29 years) in models examining risk in teenage mothers, and 5 maternal age groups for the standard maternal age analysis. The risks to teenage mothers was restricted to mothers <18 years, 18 years and 19 years as some registries had no births to mothers <=15 and/or 16 years in their population. Poisson regression

models were used to assess relative risks (RR) of NTD after adjusting for country.

The Poisson models presented relative risk (RR) estimates and 95% confidence intervals (CI) relative to the maternal age baseline group (mothers 25-29 years). Country specific relative risks were also modelled with and without maternal age correction factors. Due to multiple testing of differences between age groups in each country, some significant results will be expected by chance. Statistical analysis was conducted using STATA version 9.0 (StataCorp LP, College Station, TX, USA).

Results

The study population included 25 registries in 15 countries covering approximately 4.1 million births. Mothers <20 years accounted for 4.7% of all births, ranging from 1.0% in Switzerland to 8.6% in the UK (Figure 1).

A total of 4,207 cases of NTD excluding those with additional chromosomal anomalies were extracted from the EUROCAT database, of which 29 (0.7%) were excluded from the study as maternal age was not recorded, giving a final total of 4,178 cases with maternal age known. Livebirths accounted for 28.8% of cases, fetal deaths for 5.2% and TOPFA for 66.0% of cases. Half of the NTD cases (50.2%) were spina bifida, 38.3% were anencephalus and 11.5% were encephalocele. The total prevalence of NTD, anencephalus, encephalocele and spina bifida are presented in Table 1.

Teenage Mother Analysis

There were 193,205 births to teenage mothers in 23 registries in 13 countries participating in the teenage mother analysis. Livebirths accounted for 25.2% of cases, fetal deaths for 5.2% and TOPFA for 69.9% of cases. The total prevalence of NTD was 14.46 per 10,000 births in mothers <18 years, 12.07 in mothers aged 18 years and 11.22 in mothers aged 19 years compared to 10.17 in mothers aged 25-29 years. The mean GA at birth was 35 weeks for anencephalus cases, 36 weeks for encephalocele cases and 37 weeks for spina bifida cases. For non-TOPFA anencephalus

cases, 36.8% were <18 years, 21.1% were 18 years and 42.1% were 19 years. For non-TOPFA encephalocele, 33.3% were <18 years, 11.1% were 18 years and 55.6% were 19 years. For non-TOPFA spina bifida cases, 35.68% were <18 years, 37.8% were 18 years and 26.7% were 19 years.

Table 2 shows the relative risk (RR) of NTD in teenage mothers compared to mothers aged 25-29 years. Mothers <18 years had significantly greater risk of NTD compared to mothers 25-29 years (RR=1.42, 95% CI 1.14-1.78) and this risk remained after correcting maternal age at TOPFA to maternal age at term delivery (RR=1.31, 95% CI 1.04-1.66). Adjusting for the effect of country reduced the risk estimate slightly but it remained statistically significant (RR=1.29, 95% CI 1.03-1.63). Correcting the risk estimate for maternal age at TOPFA and country reduced the risk estimate further and was no longer statistically significant (RR=1.19, 95% CI 0.94-1.52). No statistically significant increase in risk of NTD was found for mothers aged 18 or 19 years compared to mothers aged 25-29 years.

Table 3 shows the relative risk (RR) of anencephalus in teenage mothers compared to mothers aged 25-29 years. The crude RR was statistically significant for mothers <18 years (RR=1.57, 95% CI 1.11-2.22) and mothers aged 19 years (RR=1.42, 95% CI 1.04-1.93). Adjusting the crude RR for country reduced the risk estimate for mothers <18 years from 57% to 42%, which was borderline statistically significant ($p=0.05$); and reduced the risk for mothers aged 19 years from 42% to 30% (RR=1.30, 95% CI 0.95-1.78). Correcting the risk estimates of anencephalus for the effect of maternal age at TOPFA and country reduced the risk estimates for all ages further so that they were no longer statistically significant from the baseline maternal age group (mothers 25-29 years). RR for mothers <18 years was 1.38 (95% CI 0.96-1.97) and for mothers 19 years RR was 1.28 (95% CI 0.93-1.76). Country specific RR of anencephalus are shown in Figures 2a, b and c for mothers <18 years, 18 years and 19 years compared to mothers aged 25-29 years. A significant increased risk of anencephalus in mothers <18 years

compared to mothers aged 25-29 years was found in Ireland and in Switzerland after correcting for maternal age at TOPFA.

Table 4 shows the RR of encephalocele in teenage mothers compared to the mothers aged 25-29 years. There was no significant increased risk for teenage mothers compared to the baseline maternal age group.

Table 5 shows the RR of spina bifida in teenage mothers compared to mothers 25-29 years. No significant increased risk was found for teenage mothers compared to mothers aged 25-29 years. Figures 3a, b and c show the country specific RR of spina bifida by age of mother compared to mothers aged 25-29 years. A significant increased risk of spina bifida in mothers <18 years and 18 years compared to mothers aged 25-29 years was found in Italy.

Standard Maternal Age Analysis

Table 6 shows the risks of NTD according to maternal age. Younger mothers (<25 years) have a significant increased risk of NTD compared to mothers aged 25-29 years. The risk estimate is reduced in teenage mothers after correction for maternal age at TOPFA. Correction for country and maternal age at TOPFA brings the risk estimate for teenage mothers close to 1 and is no longer statistically significant (RR=1.06, 95% CI 0.92-1.22). The increased risk remains for mothers aged 20-24 years after adjusting for maternal age at TOPFA and country (RR=1.15, 95% CI 1.05-1.26). Mothers aged 30-34 years have a reduced risk of NTD compared to mothers aged 25-29 years. This protective effect disappears after correction for maternal age at TOPFA and country (RR=0.94, 95% CI 0.86-1.02). Although not statistically significant, the risk estimates increase in mothers 35 years and older following correction of maternal age at TOPFA. The risk estimates decrease in mothers <20 years following correction for maternal age at TOPFA.

Table 7 shows the maternal age risks associated with anencephalus. A significant increased risk of anencephalus is found in younger mothers compared to the baseline group (mothers 25-29 years). Adjusting for

maternal age at TOPFA and country reduces the risk estimate in mothers <20 years from 50% to 17% which is no longer statistically significant. The increased risk in mothers 20-24 years remains after adjusting for maternal age at TOPFA and country (RR=1.27, 95% CI 1.09-1.47). The risk estimates for older mothers were close to 1 and not statistically significant. Correction for maternal age at TOPFA increases the risk estimates of anencephalus particularly for mothers 35 years and older, although these are not statistically significant, and decreases the risk estimates in mothers <20 years.

Table 8 shows the maternal age risks associated with encephalocele compared to mothers 25-29 years. No significant increased or decreased risks were found. The risk estimates, although not statistically significant decreased in mothers <20 years and increased in mothers 35 years and older following correction of maternal age at TOPFA.

Table 9 shows the maternal age risks associated with spina bifida compared to mothers 25-29 years. A significant decreased risk was found for mothers 30-34 years compared to mothers aged 25-29 years. This significant reduced risk remained after correction for maternal age at TOPFA and after adjusting for country. However, the risk disappeared when both correction factors were applied simultaneously (RR=0.93, 95% CI 0.83-1.04). Correcting for maternal age at TOPFA reduced the risk estimates in mothers <20 years and increased the risk estimates in mothers 35 years and older.

Conclusions

When risks among teenage mothers are studied, maternal age correction can make a considerable difference to risk estimates.

Overall, there is evidence that young mothers are at higher risk of anencephaly but not of spina bifida.

The excess risk of anencephaly among mothers <20 is in the order of 20% and this excess risk continues in the 20-24 age group.

The evidence that excess risk is greatest in the youngest mothers (<18 years) is not strong.

The data are compatible with a higher risk of encephalocele among young mothers, but numbers were too small to rule out a chance statistical variation.

References

- 1 EUROCAT prevalence tables: <http://www.eurocat.ulster.ac.uk/pubdata/tables.html>
- 2 Loane M, Dolk H, Morris J and a EUROCAT Working Group. Maternal age specific risk of non-chromosomal anomalies. British Journal Obstetrics & Gynaecology 2009; 116: 1111-1119
- 3 Coverage of the European Population, Birth Year 2007, by EUROCAT Full or Associate Member Registries (August 2010) <http://www.eurocat-network.eu/content/EUROCAT-Population-Table-I.pdf>
- 4 EUROCAT registry descriptions: <http://www.eurocat-network.eu/ABOUTUS/MemberRegistries/MembersAndRegistryDescriptions/AllMember>

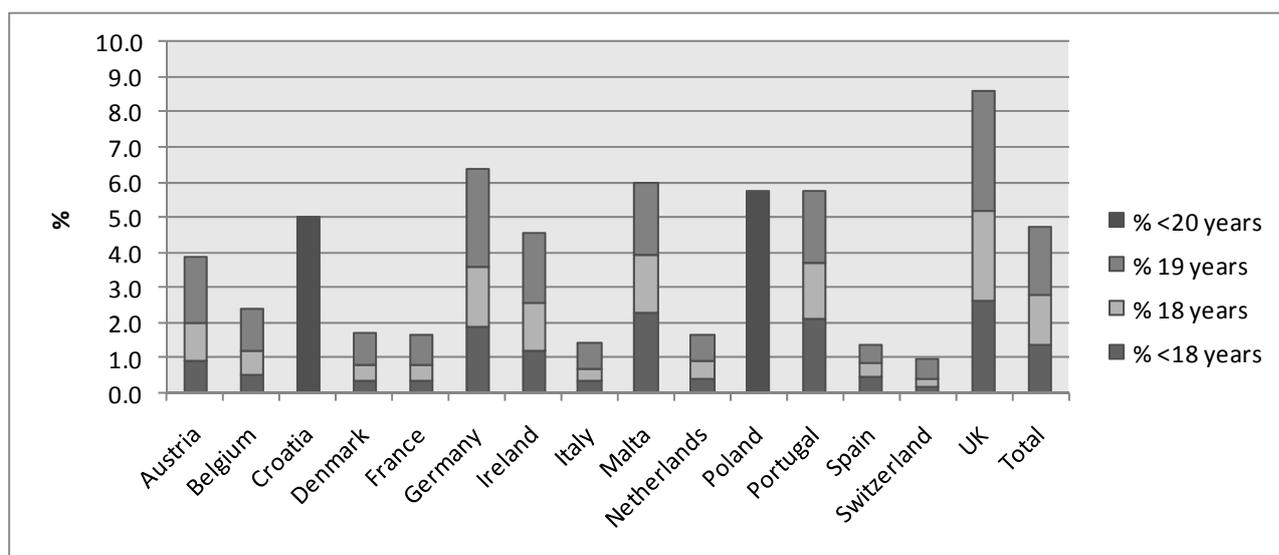
Table 1: Total prevalence (and 95% CI) of NTD, anencephalus, encephalocele and spina bifida per 10,000 births excluding chromosomal anomalies in 25 EUROCAT registries, 15 countries of Europe, 2000-2008, with maternal age known

Country	EUROCAT Registries	No NTD cases	Prevalence of NTD per 10,000 births	Prevalence of anencephalus per 10,000 births	Prevalence of encephalocele per 10,000 births	Prevalence of spina bifida per 10,000 births
Austria	Styria	82	8.77 (7.06-10.89)	1.93 (1.21-3.06)	1.71 (1.05-2.79)	5.14 (3.87-6.81)
Belgium	Antwerp	142	8.54 (7.24-10.06)	2.65 (1.97-3.55)	0.54 (0.28-1.04)	5.35 (4.35-6.58)
Croatia	Zagreb	25	4.64 (3.14-6.87)	1.67 (0.87-3.21)	1.11 (0.50-2.48)	1.86 (1.00-3.45)
Denmark	Odense	54	11.24 (8.61-14.68)	4.37 (2.85-6.70)	1.25 (0.56-2.78)	5.62 (3.85-8.20)
France	Paris, Strasbourg	417	12.70 (11.53-13.98)	5.39 (4.06-6.24)	1.71 (1.31-2.22)	5.60 (4.85-6.47)
Germany	Mainz, Saxony-Anhalt	201	11.00 (9.58-12.63)	2.74 (2.07-3.61)	1.48 (1.01-2.15)	6.79 (5.69-8.09)
Ireland	Cork and Kerry, Dublin, SE Ireland	263	8.19 (7.25-9.24)	3.08 (2.53-3.75)	0.72 (0.48-1.08)	4.39 (3.72-5.18)
Italy	Emilia Romagna, Tuscany	298	5.36 (4.79-6.01)	1.84 (1.51-2.23)	0.65 (0.47-0.90)	2.88 (2.47-3.36)
Malta	Malta	36	10.00 (7.21-13.86)	1.39 (0.58-3.34)	2.22 (1.11-4.44)	6.39 (4.25-9.61)
Netherlands	North Netherlands	116	6.71 (5.59-8.05)	1.79 (1.26-2.55)	0.58 (0.31-1.08)	4.34 (3.46-5.44)
Poland	Wielkopolska	285	10.14 (9.03-11.39)	1.89 (1.44-2.47)	1.10 (0.78-1.57)	7.15 (6.23-8.21)
Portugal	Southern Portugal	71	4.27 (3.38-5.38)	1.92 (1.36-2.72)	0.30 (0.13-0.72)	2.04 (1.46-2.86)
Spain	Barcelona, Basque Country	252	9.55 (8.45-10.81)	5.19 (4.39-6.14)	0.83 (0.55-1.27)	3.53 (2.88-4.32)

Table 1: Total prevalence (and 95% CI) of NTD, anencephalus, encephalocele and spina bifida per 10,000 births excluding chromosomal anomalies in 25 EUROCAT registries, 15 countries of Europe, 2000-2008, with maternal age known (Cont'd)

Country	EUROCAT Registries	No NTD cases	Prevalence of NTD per 10,000 births	Prevalence of anencephalus per 10,000 births	Prevalence of encephalocele per 10,000 births	Prevalence of spina bifida per 10,000 births
Switzerland	Vaud	75	11.51 (9.18-14.43)	3.99 (2.72-5.86)	2.92 (1.86-4.57)	4.60 (3.22-6.58)
UK	E Midlands & S Yorkshire, N England, Thames Valley, Wales, Wessex	1861	12.28 (11.74-12.85)	5.25 (4.89-5.62)	1.36 (1.19-1.56)	5.68 (5.31-6.07)
Total		4178	9.83 (9.54-10.13)	3.76 (3.58-3.95)	1.13 (1.03-1.24)	4.94 (4.73-5.15)

Figure 1: The proportion of births to mothers less than 20 years covered by EUROCAT registries by maternal age and country, 2000-2008*



*Information on births to mothers <math>< 20</math> years by single year of age ($\le 17</math> years, 18 years and 19 years) was available for all registries/countries for the period 2000-2008 with the exception of France, Strasbourg and Ireland, Cork & Kerry (data available for 2000-2005); Germany, Mainz (data available for 2000-2007); Italy (data available in Tuscany for 2001-2008 and Emilia Romagna for 2004-2008); Portugal (data available for 2002-2008); and Spain, Barcelona and Basque Country (data available for 2000-2007). Croatia and Poland were unable to provide the number of births to mothers <math>< 20</math> years by single year of age (Polish data available for 2000-2007 only).$

Table 2: Relative risk (and 95% CI) of NTD in younger mothers compared to baseline maternal age (mothers 25-29 years), 23 EUROCAT registries, 13 countries, 2000-2008

	Mothers <math>< 18</math> years	Mothers 18 years	Mothers 19 years	Mothers 25-29 years
Number of NTD	82	69	89	1027
Crude RR	1.42 (1.14-1.78)	1.19 (0.93-1.51)	1.10 (0.89-1.37)	1.00
Crude RR corrected	1.31 (1.04-1.66)	1.02 (0.78-1.33)	1.04 (0.83-1.30)	1.00
Adjusted* RR	1.29 (1.03-1.63)	1.08 (0.85-1.38)	1.02 (0.82-1.27)	1.00
Adjusted* RR corrected	1.19 (0.94-1.52)	0.93 (0.71-1.22)	0.96 (0.77-1.21)	1.00

RR corrected= TOPFA cases corrected for maternal age at term (40 weeks gestational age)

Adjusted*= Adjusted for country

RR= Relative Risk

CI= Confidence Intervals

Table 3: Relative risk (and 95% CI) of anencephalus in younger mothers compared to baseline maternal age (mothers 25-29 years), 13 countries, 2000-2008

	Mothers <18 years 35	Mothers 18 years 28	Mothers 19 years 44	Mothers 25-29 years 396
Number of Anencephalus				
Crude RR	1.57 (1.11-2.22)	1.25 (0.85-1.83)	1.42 (1.04-1.93)	1.00
Crude RR corrected	1.54 (1.08-2.19)	0.78 (0.48-1.27)	1.40 (1.02-1.92)	1.00
Adjusted* RR	1.42 (1.00-2.01)	1.13 (0.76-1.66)	1.30 (0.95-1.78)	1.00
Adjusted* RR corrected	1.38 (0.96-1.97)	0.70 (0.43-1.15)	1.28 (0.93-1.76)	1.00

RR corrected= TOPFA cases corrected for maternal age at term (40 weeks gestational age)

Adjusted*= Adjusted for country

RR= Relative Risk

CI= Confidence Intervals

Figure 2a: Country specific relative risks (with 95% CI) of anencephalus in mothers <18 years compared to mothers 25-29 years, 13 countries, 2000-2008

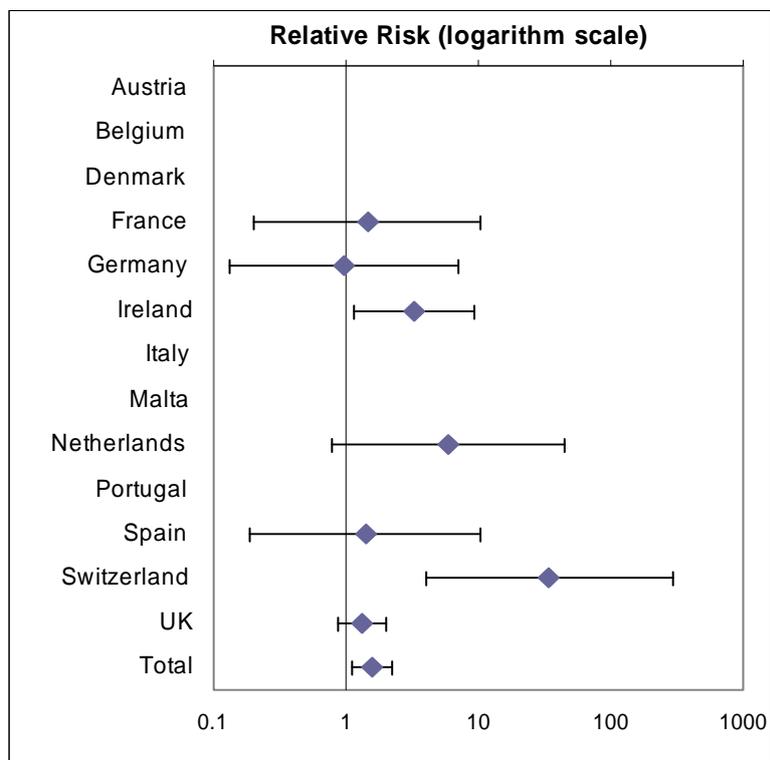


Figure 2b: Country specific relative risks (with 95% CI) of anencephalus in mothers 18 years compared to mothers 25-29 years, 13 countries, 2000-2008

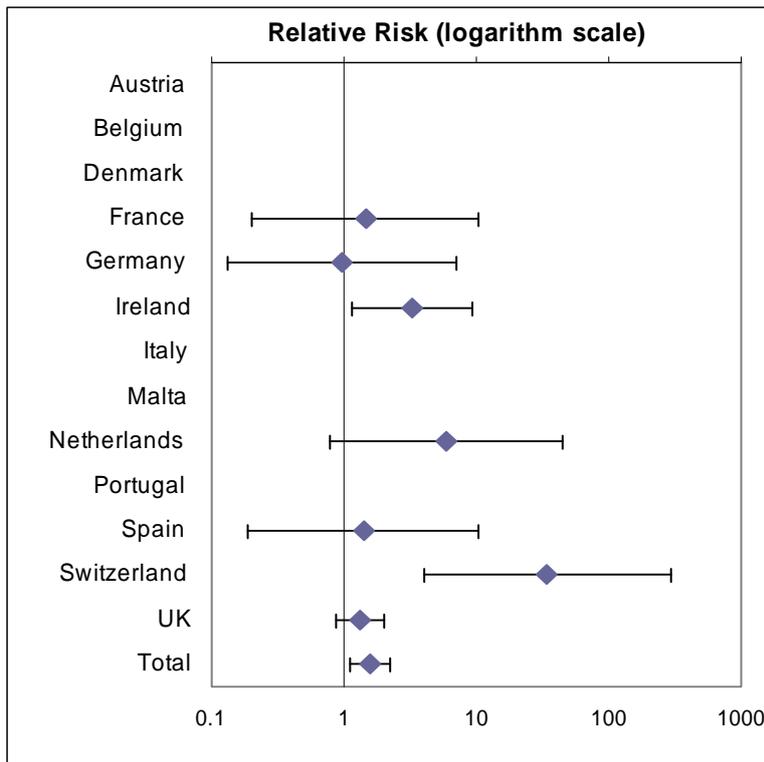


Figure 2c: Country specific relative risks (with 95% CI) of anencephalus in mothers 19 years compared to mothers 25-29 years, 13 countries, 2000-2008

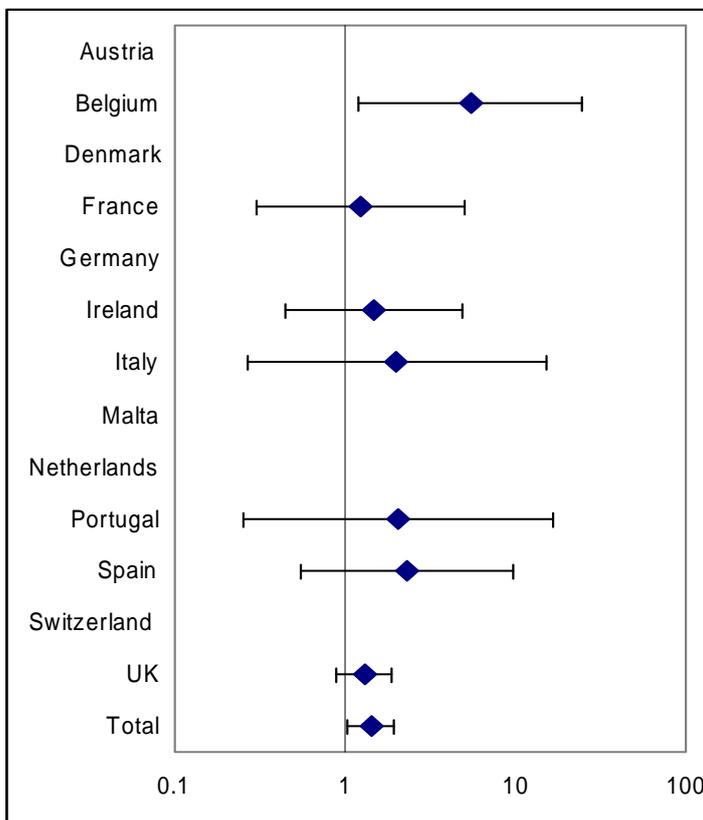


Table 4: Relative risk (and 95% CI) of encephalocele in younger mothers compared to baseline maternal age (mothers 25-29 years), 13 countries, 2000-2008

	Mothers <18 years 11	Mothers 18 years 6	Mothers 19 years 13	Mothers 25-29 years 108
Number of Encephalocele				
Crude RR	1.81 (0.98-3.37)	0.98 (0.43-2.23)	1.53 (0.86-2.73)	1.00
Crude RR corrected	1.66 (0.87-3.18)	0.99 (0.44-2.25)	1.31 (0.70-2.44)	1.00
Adjusted* RR	1.65 (0.88-3.11)	0.90 (0.39-2.05)	1.43 (0.80-2.55)	1.00
Adjusted* RR corrected	1.51 (0.78-2.91)	0.90 (0.39-2.06)	1.21 (0.65-2.27)	1.00

RR corrected= TOPFA cases corrected for maternal age at term (40 weeks gestational age)
Adjusted*= Adjusted for country
RR= Relative Risk
CI= Confidence Intervals
NS= Not statistically significant at P<0.05 level

Table 5: Relative risk (and 95% CI) of spina bifida in younger mothers compared to baseline maternal age (mothers 25-29 years), 13 countries, 2000-2008

	Mothers <18 years 36	Mothers 18 years 35	Mothers 19 years 32	Mothers 25-29 years 523
Number of Spina bifida				
Crude RR	1.23 (0.87-1.72)	1.18 (0.84-1.66)	0.78 (0.55-1.11)	1.00
Crude RR corrected	1.08 (0.75-1.55)	1.21 (0.86-1.70)	0.72 (0.50-1.05)	1.00
Adjusted* RR	1.13 (0.80-1.58)	1.09 (0.77-1.54)	0.72 (0.51-1.04)	1.00
Adjusted* RR corrected	0.99 (0.69-1.43)	1.11 (0.79-1.57)	0.67 (0.46-0.98)	1.00

RR corrected= TOPFA cases corrected for maternal age at term (40 weeks gestational age)
Adjusted*= Adjusted for country
RR= Relative Risk
CI= Confidence Intervals

Table 3a: Country specific relative risk (with 95% CI) of spina bifida in mothers <18 years compared to mothers 25-29 years, 13 countries, 2000-2008

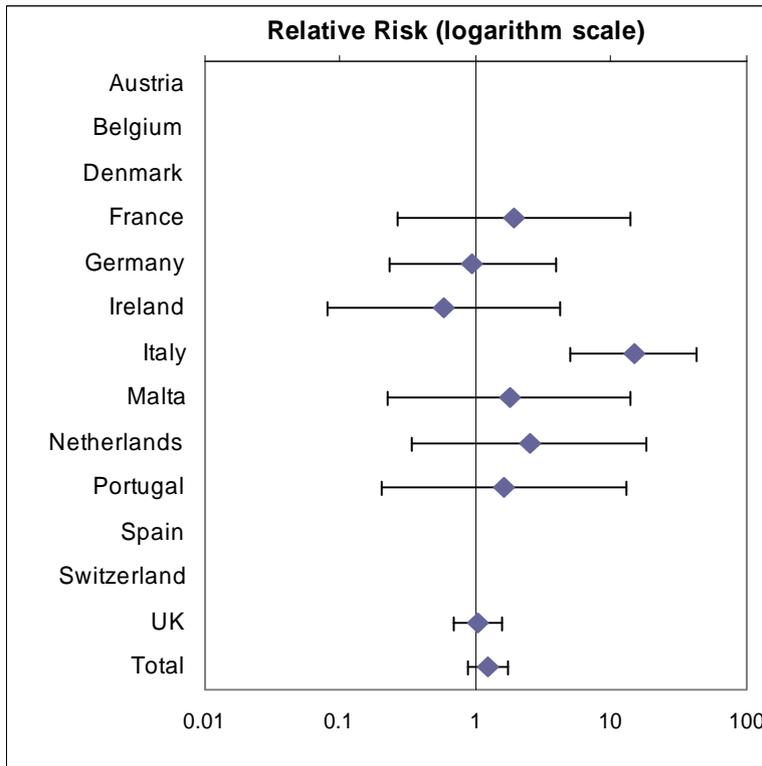


Table 3b: Country specific relative risk (with 95% CI) of spina bifida in mothers 18 years compared to mothers 25-29 years, 13 countries, 2000-2008

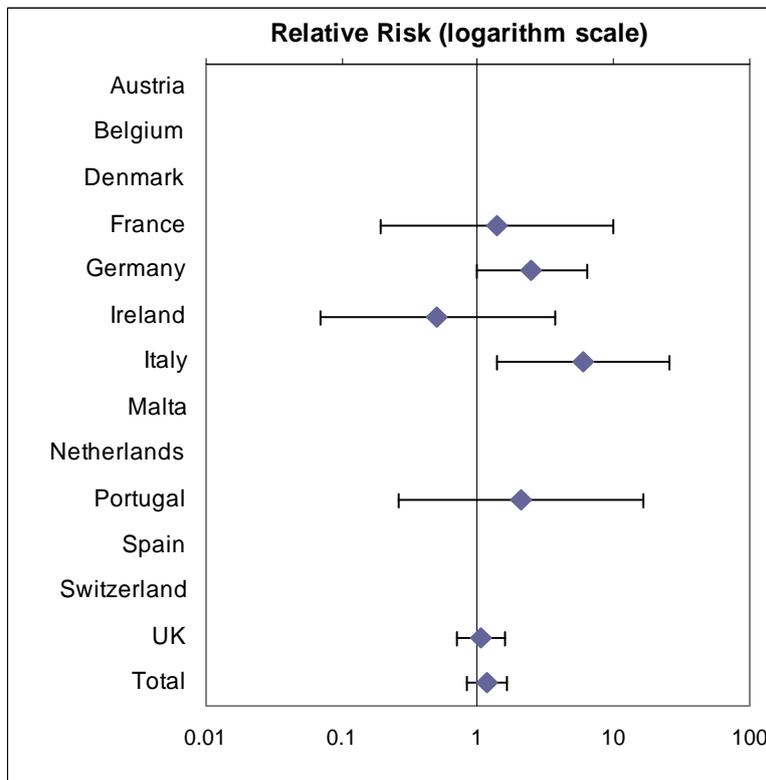


Table 3c: Country specific relative risk (with 95% CI) of spina bifida in mothers 19 years compared to mothers 25-29 years, 13 countries, 2000-2008

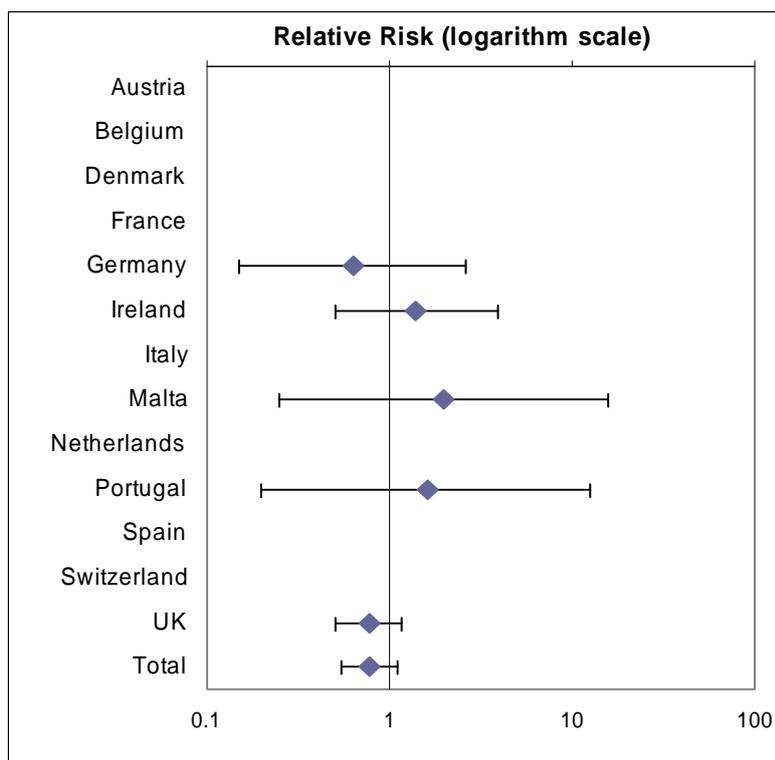


Table 6: Maternal age relative risk (and 95% CI) of NTD compared to baseline maternal age (mothers 25-29 years), 15 countries, 2000-2008

	Mothers <20	Mothers 20-24	Mothers 25-29	Mothers 30-34	Mothers 35+
Number of NTD cases	262	821	1166	1158	771
Crude RR	1.26 (1.10-1.44)	1.19 (1.09-1.31)	1.00	0.88 (0.81-0.96)	0.95 (0.86-1.04)
Crude RR corrected	1.15 (1.00-1.32)	1.20 (1.10-1.31)	1.00	0.92 (0.85-1.00)	1.01 (0.93-1.11)
Adjusted* RR	1.16 (1.01-1.33)	1.15 (1.05-1.26)	1.00	0.90 (0.83-0.97)	0.97 (0.88-1.06)
Adjusted* RR corrected	1.06 (0.92-1.22)	1.15 (1.05-1.26)	1.00	0.94 (0.86-1.02)	1.04 (0.95-1.14)

RR corrected= TOPFA cases corrected for maternal age at term (40 weeks gestational age)
 Adjusted*= Adjusted for country
 RR= Relative Risk
 CI= Confidence Intervals

Table 7: Maternal age relative risk (and 95% CI) of anencephalus compared to baseline maternal age (mothers 25-29 years), 15 countries, 2000-2008

	Mothers <20	Mothers 20-24	Mothers 25-29	Mothers 30-34	Mothers 35+
Anencephalus cases (n)	113	317	422	455	292
Crude RR	1.50 (1.22-1.84)	1.27 (1.10-1.47)	1.00	0.96 (0.84-1.09)	0.99 (0.85-1.15)
Crude RR corrected	1.33 (1.06-1.66)	1.31 (1.13-1.52)	1.00)	1.00 (0.88-1.14)	1.11 (0.96-1.28)
Adjusted* RR	1.33 (1.08-1.64)	1.24 (1.07-1.43)	1.00	0.93 (0.81-1.06)	0.94 (0.81-1.10)
Adjusted* RR corrected	1.17 (0.94-1.46)	1.27 (1.09-1.47))	1.00	0.97 (0.85-1.11)	1.06 (0.91-1.22)

RR corrected= TOPFA cases corrected for maternal age at term (40 weeks gestational age)

Adjusted*= Adjusted for country

RR= Relative Risk

CI= Confidence Intervals

Table 8: Maternal age relative risk (and 95% CI) of encephalocele compared to baseline maternal age (mothers 25-29 years), 15 countries, 2000-2008

	Mothers <20	Mothers 20-24	Mothers 25-29	Mothers 30-34	Mothers 35+
Encephalocele cases (n)	33	98	131	125	93
Crude RR	1.41 (0.96-2.06)	1.27 (0.98-1.65)	1.00	0.85 (0.66-1.08)	1.02 (0.78-1.33)
Crude RR corrected	1.29 (0.87-1.92)	1.27 (0.97-1.65)	1.00)	0.85 (0.67-1.09)	1.08 (0.83-1.40)
Adjusted* RR	1.34 (0.91-1.97)	1.23 (0.95-1.60)	1.00	0.87 (0.68-1.11)	1.04 (0.80-1.37)
Adjusted* RR corrected	1.22 (0.82-1.82)	1.23 (0.94-1.60)	1.00	0.88 (0.69-1.13)	1.11 (0.85-1.45)

RR corrected= TOPFA cases corrected for maternal age at term (40 weeks gestational age)

Adjusted*= Adjusted for country

RR= Relative Risk

CI= Confidence Intervals

Table 9: Maternal age relative risk (and 95% CI) of spina bifida compared to baseline maternal age (mothers 25-29 years), 15 countries, 2000-2008

	Mothers <20	Mothers 20-24	Mothers 25-29	Mothers 30-34	Mothers 35+
Spina bifida cases (n)	116	406	613	578	386
Crude RR	1.06 (0.87-1.29)	1.12 (0.99-1.27)	1.00	0.84 (0.75-0.94)	0.90 (0.79-1.02)
Crude RR corrected	1.00 (0.82-1.23)	1.11 (0.98-1.26)	1.00	0.88 (0.78-0.98)	0.94 (0.83-1.06)
Adjusted* RR	1.00 (0.82-1.23)	1.11 (0.98-1.26)	1.00	0.88 (0.78-0.98)	0.94 (0.83-1.06)
Adjusted* RR corrected	0.94 (0.77-1.16)	1.06 (0.93-1.21)	1.00	0.93 (0.83-1.04)	1.01 (0.89-1.15)

RR corrected= TOPFA cases corrected for maternal age at term (40 weeks gestational age)

Adjusted*= Adjusted for country

RR= Relative Risk

CI= Confidence Intervals