A

| Study ID | OR (95% CI) | % Weight |
|---|---|---|
| Cohort or RCT | | |
| Andrew E. Czeizel (2004) | 0.88 (0.27, 2.76) | 1.33 |
| Tanya Bedard (2013) | 1.52 (1.10, 2.10) | 6.25 |
| Shiliang Liu (2016) | 0.82 (0.69, 0.95) | 8.15 |
| Baohong Mao (2017) | 0.67 (0.35, 1.27) | 3.25 |
| Nina Øyen (2019) | 1.08 (0.96, 1.23) | 8.49 |
| Subtotal (I-squared = 74.0%, p = 0.004) | 1.01 (0.79, 1.29) | 27.47 |
| . | | |
| Case-control | | |
| Martha M. Werler (1999) | 1.20 (0.80, 1.80) | 5.31 |
| Ingrid M van Beynum (2010) | 0.62 (0.47, 0.82) | 6.79 |
| Adolfo Correa (2012) | 0.80 (0.65, 0.97) | 7.72 |
| Xiaohong Li (2013) | 0.39 (0.25, 0.61) | 4.88 |
| Melinda Csa´ky-Szunyogh (2013) | 0.82 (0.75, 0.91) | 8.70 |
| Melinda Csáky-Szunyogh (2014) | 0.78 (0.62, 0.99) | 7.32 |
| Andrew E. Czeizel (2015) | 0.83 (0.66, 0.97) | 7.80 |
| Elisabeth Leirgul (2015) | 1.30 (1.08, 1.56) | 7.90 |
| Yu Feng (2018) | 0.45 (0.36, 0.55) | 7.58 |
| Yanji Qu (2020) | 0.84 (0.75, 0.95) | 8.53 |
| Subtotal (I-squared = 87.7%, p = 0.000) | 0.77 (0.65, 0.91) | 72.53 |
| . | | |
| OVERALL (I-squared = 86.5%, p = 0.000) | 0.83 (0.72, 0.96) | 100.00 |

NOTE: Weights are from random effects analysis

.25 1 4

B

| Study ID | OR (95% CI) | % Weight |
|---|---|---|
| Europe or Australia | | |
| Andrew E. Czeizel (2004) | 0.88 (0.27, 2.76) | 1.33 |
| Ingrid M van Beynum (2010) | 0.62 (0.47, 0.82) | 6.79 |
| Melinda Csa´ky-Szunyogh (2013) | 0.82 (0.75, 0.91) | 8.70 |
| Melinda Csáky-Szunyogh (2014) | 0.78 (0.62, 0.99) | 7.32 |
| Andrew E. Czeizel (2015) | 0.83 (0.66, 0.97) | 7.80 |
| Elisabeth Leirgul (2015) | 1.30 (1.08, 1.56) | 7.90 |
| Nina Øyen (2019) | 1.08 (0.96, 1.23) | 8.49 |
| Subtotal (I-squared = 83.4%, p = 0.000) | 0.89 (0.75, 1.07) | 48.33 |
| . | | |
| China | | |
| Xiaohong Li (2013) | 0.39 (0.25, 0.61) | 4.88 |
| Baohong Mao (2017) | 0.67 (0.35, 1.27) | 3.25 |
| Yu Feng (2018) | 0.45 (0.36, 0.55) | 7.58 |
| Yanji Qu (2020) | 0.84 (0.75, 0.95) | 8.53 |
| Subtotal (I-squared = 90.8%, p = 0.000) | 0.56 (0.36, 0.88) | 24.25 |
| . | | |
| America | | |
| Martha M. Werler (1999) | 1.20 (0.80, 1.80) | 5.31 |
| Adolfo Correa (2012) | 0.80 (0.65, 0.97) | 7.72 |
| Tanya Bedard (2013) | 1.52 (1.10, 2.10) | 6.25 |
| Shiliang Liu (2016) | 0.82 (0.69, 0.95) | 8.15 |
| Subtotal (I-squared = 79.5%, p = 0.002) | 1.01 (0.77, 1.33) | 27.42 |
| . | | |
| OVERALL (I-squared = 86.5%, p = 0.000) | 0.83 (0.72, 0.96) | 100.00 |

NOTE: Weights are from random effects analysis

.25 1 4

C

| Study ID | OR (95% CI) | % Weight |
|---|---|---|
| 2010 or after | | |
| Andrew E. Czeizel (2004) | 0.88 (0.27, 2.76) | 1.33 |
| Ingrid M van Beynum (2010) | 0.62 (0.47, 0.82) | 6.79 |
| Adolfo Correa (2012) | 0.80 (0.65, 0.97) | 7.72 |
| Xiaohong Li (2013) | 0.39 (0.25, 0.61) | 4.88 |
| Melinda Csa´ky-Szunyogh (2013) | 0.82 (0.75, 0.91) | 8.70 |
| Tanya Bedard (2013) | 1.52 (1.10, 2.10) | 6.25 |
| Melinda Csáky-Szunyogh (2014) | 0.78 (0.62, 0.99) | 7.32 |
| Andrew E. Czeizel (2015) | 0.83 (0.66, 0.97) | 7.80 |
| Elisabeth Leirgul (2015) | 1.30 (1.08, 1.56) | 7.90 |
| Shiliang Liu (2016) | 0.82 (0.69, 0.95) | 8.15 |
| Baohong Mao (2017) | 0.67 (0.35, 1.27) | 3.25 |
| Yu Feng (2018) | 0.45 (0.36, 0.55) | 7.58 |
| Nina Øyen (2019) | 1.08 (0.96, 1.23) | 8.49 |
| Yanji Qu (2020) | 0.84 (0.75, 0.95) | 8.53 |
| Subtotal (I-squared = 87.1%, p = 0.000) | 0.81 (0.70, 0.94) | 94.69 |
| . | | |
| Before 2010 | | |
| Martha M. Werler (1999) | 1.20 (0.80, 1.80) | 5.31 |
| Subtotal (I-squared = .%, p = .) | 1.20 (0.80, 1.80) | 5.31 |
| . | | |
| OVERALL (I-squared = 86.5%, p = 0.000) | 0.83 (0.72, 0.96) | 100.00 |

NOTE: Weights are from random effects analysis

.25 1 4

D

| Study ID | OR (95% CI) | % Weight |
|---|---|---|
| High | | |
| Martha M. Werler (1999) | 1.20 (0.80, 1.80) | 5.31 |
| Ingrid M van Beynum (2010) | 0.62 (0.47, 0.82) | 6.79 |
| Xiaohong Li (2013) | 0.39 (0.25, 0.61) | 4.88 |
| Melinda Csa´ky-Szunyogh (2013) | 0.82 (0.75, 0.91) | 8.70 |
| Andrew E. Czeizel (2015) | 0.83 (0.66, 0.97) | 7.80 |
| Elisabeth Leirgul (2015) | 1.30 (1.08, 1.56) | 7.90 |
| Baohong Mao (2017) | 0.67 (0.35, 1.27) | 3.25 |
| Yu Feng (2018) | 0.45 (0.36, 0.55) | 7.58 |
| Nina Øyen (2019) | 1.08 (0.96, 1.23) | 8.49 |
| Yanji Qu (2020) | 0.84 (0.75, 0.95) | 8.53 |
| Subtotal (I-squared = 90.0%, p = 0.000) | 0.79 (0.65, 0.95) | 69.23 |
| . | | |
| Low | | |
| Andrew E. Czeizel (2004) | 0.88 (0.27, 2.76) | 1.33 |
| Adolfo Correa (2012) | 0.80 (0.65, 0.97) | 7.72 |
| Tanya Bedard (2013) | 1.52 (1.10, 2.10) | 6.25 |
| Melinda Csáky-Szunyogh (2014) | 0.78 (0.62, 0.99) | 7.32 |
| Shiliang Liu (2016) | 0.82 (0.69, 0.95) | 8.15 |
| Subtotal (I-squared = 70.2%, p = 0.009) | 0.91 (0.73, 1.13) | 30.77 |
| . | | |
| OVERALL (I-squared = 86.5%, p = 0.000) | 0.83 (0.72, 0.96) | 100.00 |

NOTE: Weights are from random effects analysis

.25 1 4