ADDITIONAL FILE 3
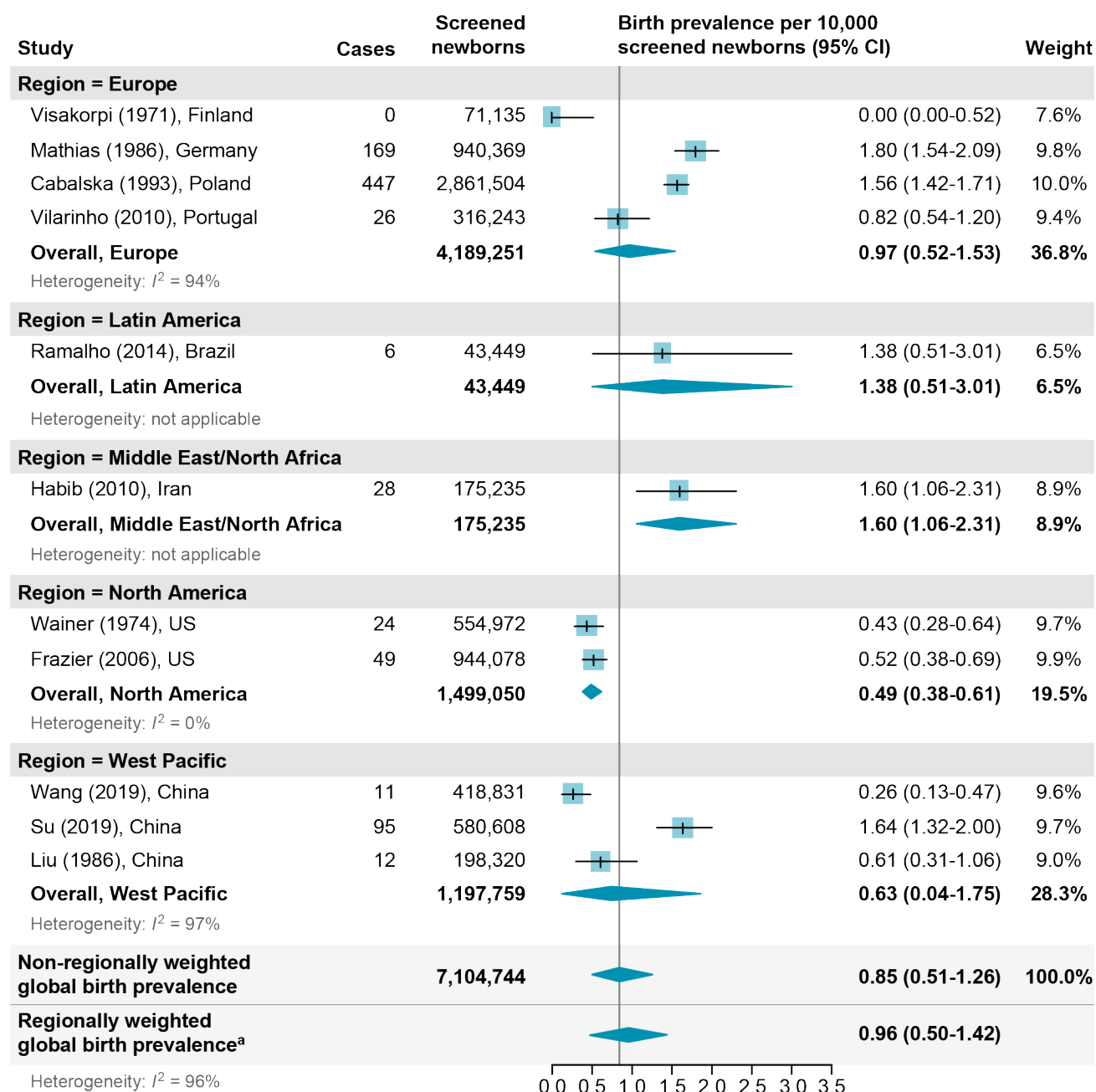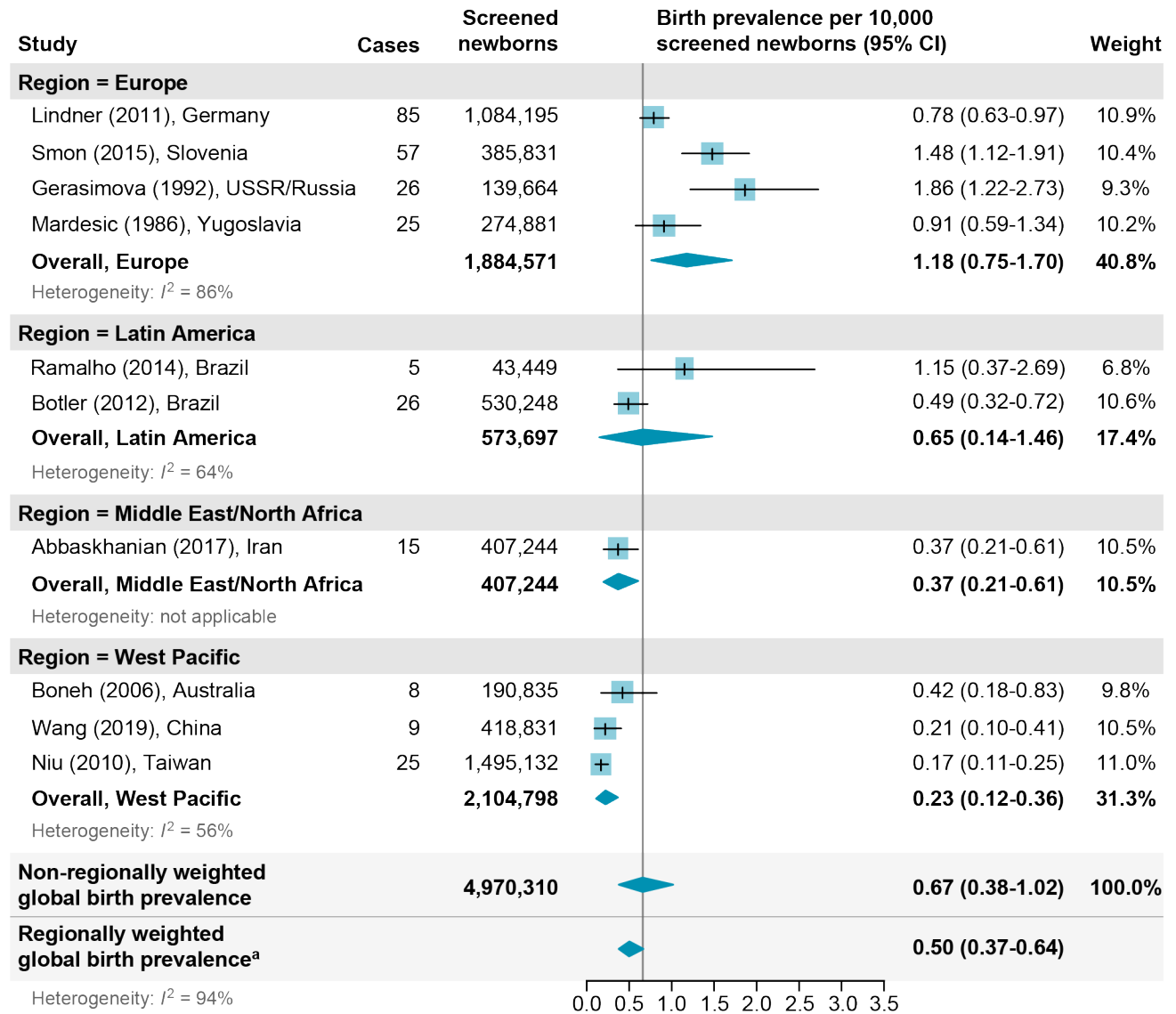
Figure A-2. Meta-Analysis Results by Region: Confirmatory Test Phenylalanine Cutoff Value of 360 ± 100 µmol/L

Study	Cases	Screened newborns	Birth prevalence per 10,000 screened newborns (95% CI)	Weight
Region = Europe				
Visakorpi (1971), Finland	0	71,135	0.00 (0.00-0.52)	7.6%
Mathias (1986), Germany	169	940,369	1.80 (1.54-2.09)	9.8%
Cabalska (1993), Poland	447	2,861,504	1.56 (1.42-1.71)	10.0%
Vilarinho (2010), Portugal	26	316,243	0.82 (0.54-1.20)	9.4%
Overall, Europe		**4,189,251**	**0.97 (0.52-1.53)**	**36.8%**
Heterogeneity: I^2 = 94%				
Region = Latin America				
Ramalho (2014), Brazil	6	43,449	1.38 (0.51-3.01)	6.5%
Overall, Latin America		**43,449**	**1.38 (0.51-3.01)**	**6.5%**
Heterogeneity: not applicable				
Region = Middle East/North Africa				
Habib (2010), Iran	28	175,235	1.60 (1.06-2.31)	8.9%
Overall, Middle East/North Africa		**175,235**	**1.60 (1.06-2.31)**	**8.9%**
Heterogeneity: not applicable				
Region = North America				
Wainer (1974), US	24	554,972	0.43 (0.28-0.64)	9.7%
Frazier (2006), US	49	944,078	0.52 (0.38-0.69)	9.9%
Overall, North America		**1,499,050**	**0.49 (0.38-0.61)**	**19.5%**
Heterogeneity: I^2 = 0%				
Region = West Pacific				
Wang (2019), China	11	418,831	0.26 (0.13-0.47)	9.6%
Su (2019), China	95	580,608	1.64 (1.32-2.00)	9.7%
Liu (1986), China	12	198,320	0.61 (0.31-1.06)	9.0%
Overall, West Pacific		**1,197,759**	**0.63 (0.04-1.75)**	**28.3%**
Heterogeneity: I^2 = 97%				
Non-regionally weighted global birth prevalence		**7,104,744**	**0.85 (0.51-1.26)**	**100.0%**
Regionally weighted global birth prevalence[a]			**0.96 (0.50-1.42)**	
Heterogeneity: I^2 = 96%				

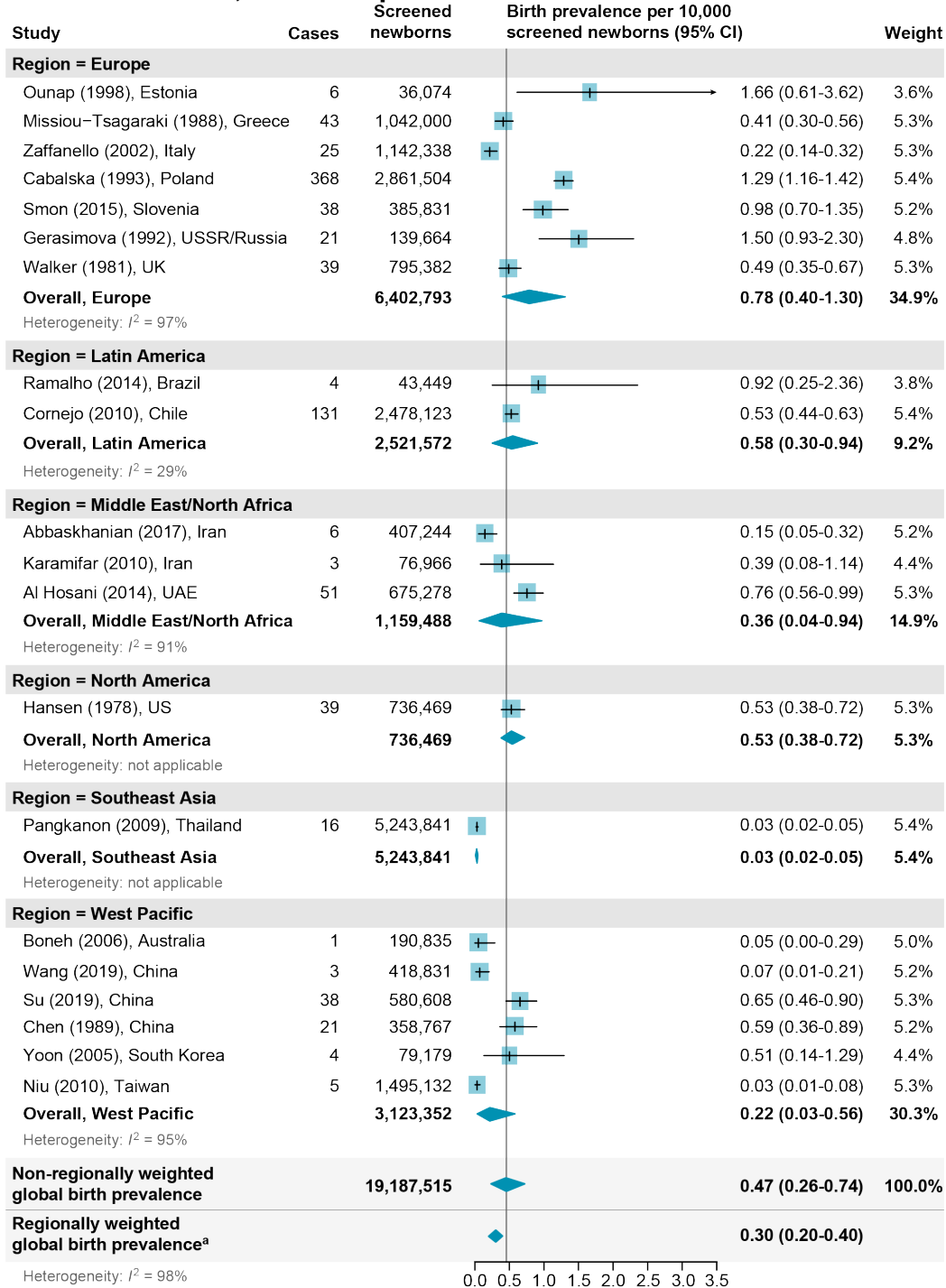x-axis: 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5

[a] The regionally weighted global prevalence was not produced directly as part of the meta-analysis but was calculated by taking a weighted average of the meta-analysis results for each of the regions, weighting them by the relative population size of each of these regions. We have added this prevalence estimate to the figure to facilitate comparison with the non-regionally weighted overall estimate from the meta-analysis.

Figure A-3. Meta-Analysis Results by Region: Confirmatory Test Phenylalanine Cutoff Value of 600 ± 100 µmol/L

Study	Cases	Screened newborns	Birth prevalence per 10,000 screened newborns (95% CI)	Weight
Region = Europe				
Lindner (2011), Germany	85	1,084,195	0.78 (0.63-0.97)	10.9%
Smon (2015), Slovenia	57	385,831	1.48 (1.12-1.91)	10.4%
Gerasimova (1992), USSR/Russia	26	139,664	1.86 (1.22-2.73)	9.3%
Mardesic (1986), Yugoslavia	25	274,881	0.91 (0.59-1.34)	10.2%
Overall, Europe		**1,884,571**	**1.18 (0.75-1.70)**	**40.8%**
Heterogeneity: I^2 = 86%				
Region = Latin America				
Ramalho (2014), Brazil	5	43,449	1.15 (0.37-2.69)	6.8%
Botler (2012), Brazil	26	530,248	0.49 (0.32-0.72)	10.6%
Overall, Latin America		**573,697**	**0.65 (0.14-1.46)**	**17.4%**
Heterogeneity: I^2 = 64%				
Region = Middle East/North Africa				
Abbaskhanian (2017), Iran	15	407,244	0.37 (0.21-0.61)	10.5%
Overall, Middle East/North Africa		**407,244**	**0.37 (0.21-0.61)**	**10.5%**
Heterogeneity: not applicable				
Region = West Pacific				
Boneh (2006), Australia	8	190,835	0.42 (0.18-0.83)	9.8%
Wang (2019), China	9	418,831	0.21 (0.10-0.41)	10.5%
Niu (2010), Taiwan	25	1,495,132	0.17 (0.11-0.25)	11.0%
Overall, West Pacific		**2,104,798**	**0.23 (0.12-0.36)**	**31.3%**
Heterogeneity: I^2 = 56%				
Non-regionally weighted global birth prevalence		**4,970,310**	**0.67 (0.38-1.02)**	**100.0%**
Regionally weighted global birth prevalence[a]			**0.50 (0.37-0.64)**	
Heterogeneity: I^2 = 94%				

Birth prevalence per 10,000 screened newborns (95% CI) axis: 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5

[a] The regionally weighted global prevalence was not produced directly as part of the meta-analysis but was calculated by taking a weighted average of the meta-analysis results for each of the regions, weighting them by the relative population size of each of these regions. We have added this prevalence estimate to the figure to facilitate comparison with the non-regionally weighted overall estimate from the meta-analysis.

Figure A-4. Meta-Analysis Results by Region: Confirmatory Test Phenylalanine Cutoff Value of 1,200 ± 200 µmol/L

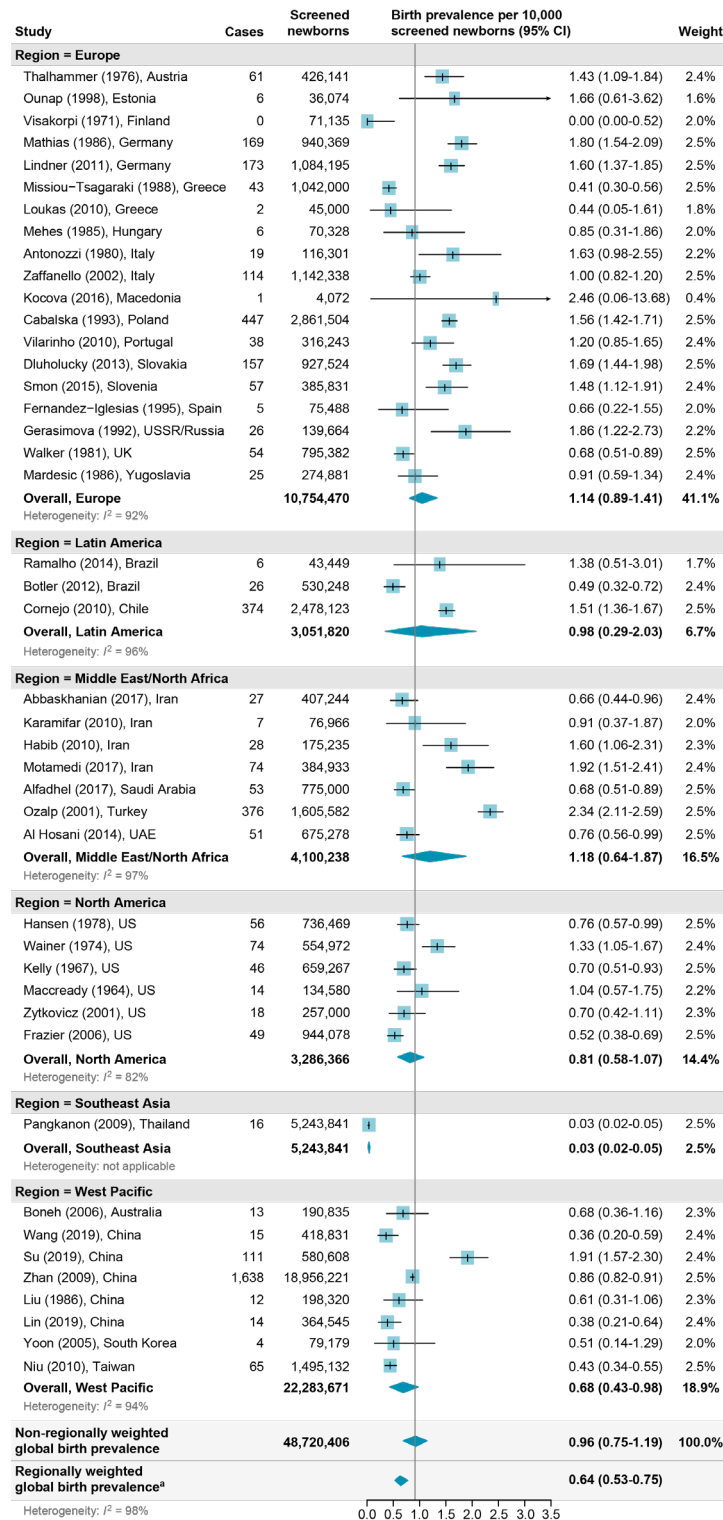| Study	Cases	Screened newborns	Birth prevalence per 10,000 screened newborns (95% CI)		Weight
Region = Europe					
Ounap (1998), Estonia	6	36,074		1.66 (0.61-3.62)	3.6%
Missiou−Tsagaraki (1988), Greece	43	1,042,000		0.41 (0.30-0.56)	5.3%
Zaffanello (2002), Italy	25	1,142,338		0.22 (0.14-0.32)	5.3%
Cabalska (1993), Poland	368	2,861,504		1.29 (1.16-1.42)	5.4%
Smon (2015), Slovenia	38	385,831		0.98 (0.70-1.35)	5.2%
Gerasimova (1992), USSR/Russia	21	139,664		1.50 (0.93-2.30)	4.8%
Walker (1981), UK	39	795,382		0.49 (0.35-0.67)	5.3%
Overall, Europe		**6,402,793**		**0.78 (0.40-1.30)**	**34.9%**
Heterogeneity: I^2 = 97%					
Region = Latin America					
Ramalho (2014), Brazil	4	43,449		0.92 (0.25-2.36)	3.8%
Cornejo (2010), Chile	131	2,478,123		0.53 (0.44-0.63)	5.4%
Overall, Latin America		**2,521,572**		**0.58 (0.30-0.94)**	**9.2%**
Heterogeneity: I^2 = 29%					
Region = Middle East/North Africa					
Abbaskhanian (2017), Iran	6	407,244		0.15 (0.05-0.32)	5.2%
Karamifar (2010), Iran	3	76,966		0.39 (0.08-1.14)	4.4%
Al Hosani (2014), UAE	51	675,278		0.76 (0.56-0.99)	5.3%
Overall, Middle East/North Africa		**1,159,488**		**0.36 (0.04-0.94)**	**14.9%**
Heterogeneity: I^2 = 91%					
Region = North America					
Hansen (1978), US	39	736,469		0.53 (0.38-0.72)	5.3%
Overall, North America		**736,469**		**0.53 (0.38-0.72)**	**5.3%**
Heterogeneity: not applicable					
Region = Southeast Asia					
Pangkanon (2009), Thailand	16	5,243,841		0.03 (0.02-0.05)	5.4%
Overall, Southeast Asia		**5,243,841**		**0.03 (0.02-0.05)**	**5.4%**
Heterogeneity: not applicable					
Region = West Pacific					
Boneh (2006), Australia	1	190,835		0.05 (0.00-0.29)	5.0%
Wang (2019), China	3	418,831		0.07 (0.01-0.21)	5.2%
Su (2019), China	38	580,608		0.65 (0.46-0.90)	5.3%
Chen (1989), China	21	358,767		0.59 (0.36-0.89)	5.2%
Yoon (2005), South Korea	4	79,179		0.51 (0.14-1.29)	4.4%
Niu (2010), Taiwan	5	1,495,132		0.03 (0.01-0.08)	5.3%
Overall, West Pacific		**3,123,352**		**0.22 (0.03-0.56)**	**30.3%**
Heterogeneity: I^2 = 95%					
Non-regionally weighted global birth prevalence		**19,187,515**		**0.47 (0.26-0.74)**	**100.0%**
Regionally weighted global birth prevalence[a]				**0.30 (0.20-0.40)**	
Heterogeneity: I^2 = 98%			0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5		

[a] The regionally weighted global prevalence was not produced directly as part of the meta-analysis but was calculated by taking a weighted average of the meta-analysis results for each of the regions, weighting them by the relative population size of each of these regions. We have added this prevalence estimate to the figure to facilitate comparison with the non-regionally weighted overall estimate from the meta-analysis.

Figure A-5. Meta-Analysis Results by Region: Overall Analysis

Study	Cases	Screened newborns	Birth prevalence per 10,000 screened newborns (95% CI)	Weight
Region = Europe				
Thalhammer (1976), Austria	61	426,141	1.43 (1.09-1.84)	2.4%
Ounap (1998), Estonia	6	36,074	1.66 (0.61-3.62)	1.6%
Visakorpi (1971), Finland	0	71,135	0.00 (0.00-0.52)	2.0%
Mathias (1986), Germany	169	940,369	1.80 (1.54-2.09)	2.5%
Lindner (2011), Germany	173	1,084,195	1.60 (1.37-1.85)	2.5%
Missiou−Tsagaraki (1988), Greece	43	1,042,000	0.41 (0.30-0.56)	2.5%
Loukas (2010), Greece	2	45,000	0.44 (0.05-1.61)	1.8%
Mehes (1985), Hungary	6	70,328	0.85 (0.31-1.86)	2.0%
Antonozzi (1980), Italy	19	116,301	1.63 (0.98-2.55)	2.2%
Zaffanello (2002), Italy	114	1,142,338	1.00 (0.82-1.20)	2.5%
Kocova (2016), Macedonia	1	4,072	2.46 (0.06-13.68)	0.4%
Cabalska (1993), Poland	447	2,861,504	1.56 (1.42-1.71)	2.5%
Vilarinho (2010), Portugal	38	316,243	1.20 (0.85-1.65)	2.4%
Dluholucky (2013), Slovakia	157	927,524	1.69 (1.44-1.98)	2.5%
Smon (2015), Slovenia	57	385,831	1.48 (1.12-1.91)	2.4%
Fernandez−Iglesias (1995), Spain	5	75,488	0.66 (0.22-1.55)	2.0%
Gerasimova (1992), USSR/Russia	26	139,664	1.86 (1.22-2.73)	2.2%
Walker (1981), UK	54	795,382	0.68 (0.51-0.89)	2.5%
Mardesic (1986), Yugoslavia	25	274,881	0.91 (0.59-1.34)	2.4%
Overall, Europe		**10,754,470**	**1.14 (0.89-1.41)**	**41.1%**
Heterogeneity: I^2 = 92%				
Region = Latin America				
Ramalho (2014), Brazil	6	43,449	1.38 (0.51-3.01)	1.7%
Botler (2012), Brazil	26	530,248	0.49 (0.32-0.72)	2.4%
Cornejo (2010), Chile	374	2,478,123	1.51 (1.36-1.67)	2.5%
Overall, Latin America		**3,051,820**	**0.98 (0.29-2.03)**	**6.7%**
Heterogeneity: I^2 = 96%				
Region = Middle East/North Africa				
Abbaskhanian (2017), Iran	27	407,244	0.66 (0.44-0.96)	2.4%
Karamifar (2010), Iran	7	76,966	0.91 (0.37-1.87)	2.0%
Habib (2010), Iran	28	175,235	1.60 (1.06-2.31)	2.3%
Motamedi (2017), Iran	74	384,933	1.92 (1.51-2.41)	2.4%
Alfadhel (2017), Saudi Arabia	53	775,000	0.68 (0.51-0.89)	2.5%
Ozalp (2001), Turkey	376	1,605,582	2.34 (2.11-2.59)	2.5%
Al Hosani (2014), UAE	51	675,278	0.76 (0.56-0.99)	2.5%
Overall, Middle East/North Africa		**4,100,238**	**1.18 (0.64-1.87)**	**16.5%**
Heterogeneity: I^2 = 97%				
Region = North America				
Hansen (1978), US	56	736,469	0.76 (0.57-0.99)	2.5%
Wainer (1974), US	74	554,972	1.33 (1.05-1.67)	2.4%
Kelly (1967), US	46	659,267	0.70 (0.51-0.93)	2.5%
Maccready (1964), US	14	134,580	1.04 (0.57-1.75)	2.2%
Zytkovicz (2001), US	18	257,000	0.70 (0.42-1.11)	2.3%
Frazier (2006), US	49	944,078	0.52 (0.38-0.69)	2.5%
Overall, North America		**3,286,366**	**0.81 (0.58-1.07)**	**14.4%**
Heterogeneity: I^2 = 82%				
Region = Southeast Asia				
Pangkanon (2009), Thailand	16	5,243,841	0.03 (0.02-0.05)	2.5%
Overall, Southeast Asia		**5,243,841**	**0.03 (0.02-0.05)**	**2.5%**
Heterogeneity: not applicable				
Region = West Pacific				
Boneh (2006), Australia	13	190,835	0.68 (0.36-1.16)	2.3%
Wang (2019), China	15	418,831	0.36 (0.20-0.59)	2.4%
Su (2019), China	111	580,608	1.91 (1.57-2.30)	2.4%
Zhan (2009), China	1,638	18,956,221	0.86 (0.82-0.91)	2.5%
Liu (1986), China	12	198,320	0.61 (0.31-1.06)	2.3%
Lin (2019), China	14	364,545	0.38 (0.21-0.64)	2.4%
Yoon (2005), South Korea	4	79,179	0.51 (0.14-1.29)	2.0%
Niu (2010), Taiwan	65	1,495,132	0.43 (0.34-0.55)	2.5%
Overall, West Pacific		**22,283,671**	**0.68 (0.43-0.98)**	**18.9%**
Heterogeneity: I^2 = 94%				
Non-regionally weighted global birth prevalence		**48,720,406**	**0.96 (0.75-1.19)**	**100.0%**
Regionally weighted global birth prevalence[a]			**0.64 (0.53-0.75)**	
Heterogeneity: I^2 = 98%				

0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5

[a] The regionally weighted global prevalence was not produced directly as part of the meta-analysis but was calculated by taking a weighted average of the meta-analysis results for each of the regions, weighting them by the relative population size of each of these regions. We have added this prevalence estimate to the figure to facilitate comparison with the non-regionally weighted overall estimate from the meta-analysis.