Newcastle-Otta	awa Assessme	ent scale of eleven of	case-control s	tudies	
Reference	Selection	Selection Comparability		Overall score	
Hao et al 2015	***	**	*	6 stars	
Sabbagh et al 2015	***	**	**	7 stars	
Hoyt et al 2016	***	_	*	4 stars	
Kummet et al 2016	***	**	**	7 stars	
Mckinney et al 2016	**	**	*	5stars	
Dien et al 2017	**	**	*	5 stars	
Goveas et al 2017	**	_	*	3 stars	
Junaid et al 2017	**	**	*	5 stars	
Pi et al 2018	**	**	*	5 stars	
Altoe et al 2019	-	*	**	3 stars	
Chowchuen et al 2020	**	-	*	3 stars	
Newcast	le-Ottawa As	sessment scale of C	ohort studies		
Reference	Selection	Comparability	Outcome	Overall score	
Sato et al 2021	***	*	*	5 stars	

Supplementary Table 1. Summary of Newcastle-Ottawa Assessment scale of included studies.

Supplementary Table 2. Egger's Regression-Based Test.

Parameter	Coefficient	Std. Error	t	p-value		95% CI
(Intercept)	.352	.2345	1.501	.146	131	.835
SE	1.103	1.0386	1.062	.298	-1.036	3.243

Random-effects meta-regression

SE Standard error of effect size

Covariate	Ref	Coefficient	SE	959	% CI	t- value	P- value	VIF
Intercept		0.4888	0.1063	0.2741	0.7034	4.6	0	2.649
Year: >=2013	<2013	-0.6038	0.1754	-0.9581	-0.2495	-3.44	0.0013	1.756
Low quality	High quality	0.727	0.1742	0.3752	1.0788	4.17	0.0002	1.758
Passive smoking	Active smoking	-0.1257	0.1449	-0.4183	0.167	-0.87	0.3909	1.036

Supplementary Table 3. Meta-regression random effects (REML) model.

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero

F = 6.51, df = 3, 41, p = 0.0011

Goodness of fit: Test that unexplained variance is zero

 $Tau^2 = 0.1177$, Tau = 0.3430, $I^2 = 79.39\%$, Q = 198.98, df = 41, p = 0.0000

Comparison of Model 1 with the null model

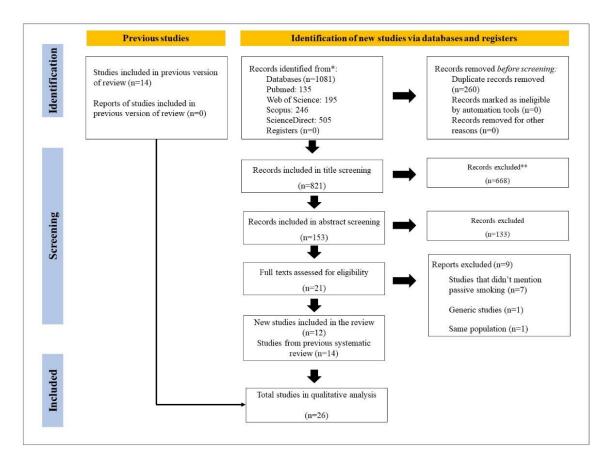
Total between-study variance (intercept only)

 $Tau^2 = 0.1768$, Tau = 0.4205, $I^2 = 83.14\%$, Q = 261.03, df = 44, p = 0.0000

The proportion of total between-study variance explained by Model 1

 R^2 analog = 0.33

Supplementary Figure 1. PRISMA 2020 flow diagram for updated systematic reviews which included searches of databases and registers only.



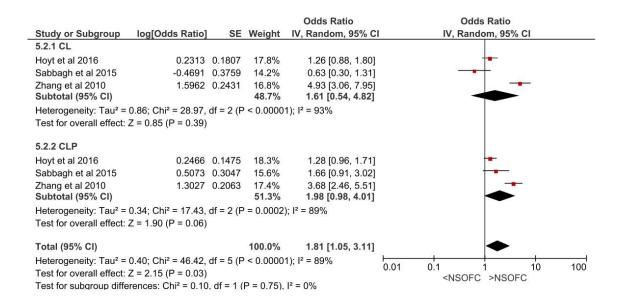
*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

For more information, visit: http://www.prisma-statement.org/

Supplementary Figure 2. Forest plot for meta-analysis of the association between maternal environmental tobacco exposure and the risk of having an infant NSOFC sub-grouped according to CL/P phenotypes (CLP and CP).



Supplementary Figure 3. Forest plot for meta-analysis of the association between the risk of having an infant with NSOFC and its association with maternal active smoking.

	NSOF		Con	trol		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	r M-H, Random, 95% Cl
Beaty et al 2001	27	135	25	182	6.5%	1.57 [0.86, 2.85]	2001	1 +
Little et al 2004	80	190	59	189	8.9%	1.60 [1.05, 2.44]	2004	1 -
Honein et al 2007	352	1461	684	3390	13.1%	1.26 [1.08, 1.45]	2007	*
Chevrier et al 2008	27	171	25	182	6.6%	1.18 [0.65, 2.12]	2008	3
Lie et al 2008	239	432	243	763	11.7%	2.65 [2.08, 3.38]	2008	3 -
Leite and Koifman 2009	51	274	88	547	9.5%	1.19 [0.82, 1.74]	2009) +
Wang et al 2009	12	344	16	1172	4.9%	2.61 [1.22, 5.57]	2009	
Zhang et al 2010	14	300	6	454	3.5%	3.66 [1.39, 9.62]	2010) — —
Jia et al 2011	18	713	2	221	1.7%	2.84 [0.65, 12.32]	2011	
Mirilas et al 2011	6	35	7	35	2.4%	0.83 [0.25, 2.77]	2011	· · · · · · · · · · · · · · · · · · ·
Taghavi et al 2012	7	300	5	300	2.6%	1.41 [0.44, 4.49]	2012	2
Hao et al 2015	35	499	28	480	7.5%	1.22 [0.73, 2.03]	2015	5
Sabbagh et al 2015	6	204	10	244	3.1%	0.71 [0.25, 1.99]	2015	5
Mckinney et al 2016	93	95	92	95	1.2%	1.52 [0.25, 9.29]	2016	; · · · ·
Junaid et al 2017	1	50	1	50	0.5%	1.00 [0.06, 16.44]	2017	· · · · · · · · · · · · · · · · · · ·
Altoe et al 2019	13	150	15	300	4.8%	1.80 [0.83, 3.89]	2019	
Chowchuen et al 2020	1	34	1	70	0.5%	2.09 [0.13, 34.48]	2020)
Sato et al 2021	83	187	38228	94174	11.0%	1.17 [0.88, 1.56]	2021	ı † −
Total (95% CI)		5574		102848	100.0%	1.51 [1.23, 1.86]		•
Total events	1065		39535					
Heterogeneity: Tau ² = 0.0	8; Chi ² = 4	1.42, d	f = 17 (P	= 0.0008); l² = 59%			
Test for overall effect: Z =	3.92 (P <	0.0001)					<pre></pre>

Supplementary Figure 4. Forest plot for meta-analysis of the association between the risk of having an infant with NSOFC and its association with paternal active smoking compared to maternal environmental tobacco smoking.

	NSOF		Contr			Odds Ratio		Odds Ratio
Study or Subgroup		Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% CI
4.1.1 Paternal smoki	-							
Little et al 2004	36	91	28	119	5.0%	2.13 [1.17, 3.86]		
Wang et al 2009	178	334	330	1172	6.3%	2.91 [2.27, 3.74]	2009	
Jianyan et al 2010	105	200	91	200	5.8%	1.32 [0.89, 1.96]	2010) – –
Zhang et al 2010	110	167	325	537	5.9%	1.26 [0.88, 1.81]	2010	
Jia et al 2011	435	713	98	221	6.1%	1.96 [1.45, 2.66]	2011	
Li et al 2011	22	35	20	35	3.7%	1.27 [0.49, 3.31]	2011	
Sabbagh et al 2015	74	204	90	244	5.9%	0.97 [0.66, 1.43]	2015	· · · ·
Hao et al 2015	218	362	82	137	5.8%	1.02 [0.68, 1.52]	2015	; —
Junaid et al 2017	20	50	16	50	4.2%	1.42 [0.62, 3.22]	2017	
Subtotal (95% CI)		2156		2715	48.7%	1.51 [1.11, 2.06]		◆
Total events	1198		1080					
Heterogeneity: Tau ² =	0.16; Chi2	= 38.20	6, df = 8 (P < 0.0	00001); l ² =	= 79%		
Test for overall effect:	Z = 2.65 (P = 0.00	08)					
4.1.2 ETS								
Little et al 2004	67	154	111	189	5.7%	0.54 [0.35, 0.83]		
Wang et al 2009	168	586	192	1172	6.3%	2.05 [1.62, 2.60]		
Jianyan et al 2010	121	200	87	200	5.8%	1.99 [1.34, 2.96]		
Zhang et al 2010	224	323	169	454	6.1%	3.82 [2.82, 5.17]		
Li et al 2011	69	162	54	204	5.7%	2.06 [1.33, 3.20]	2011	
Jia et al 2011	402	713	27	221	5.7%	9.29 [6.05, 14.26]	2011	
Sabbagh et al 2015	45	204	47	244	5.6%	1.19 [0.75, 1.88]	2015	;
Hao et al 2015	285	499	175	480	6.3%	2.32 [1.80, 3.00]	2015)
Hao et al 2015 Junaid et al 2017	285 24	50	175 12	50	4.0%	2.92 [1.24, 6.87]		
Hao et al 2015								
Hao et al 2015 Junaid et al 2017		50		50	4.0%	2.92 [1.24, 6.87]		
Hao et al 2015 Junaid et al 2017 Subtotal (95% CI)	24 1405	50 2891	12 874	50 3214	4.0% 51.3%	2.92 [1.24, 6.87] 2.21 [1.42, 3.45]		
Hao et al 2015 Junaid et al 2017 Subtotal (95% CI) Total events	24 1405 0.41; Chi²	50 2891 = 105.0	12 874 00, df = 8	50 3214	4.0% 51.3%	2.92 [1.24, 6.87] 2.21 [1.42, 3.45]		
Hao et al 2015 Junaid et al 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	24 1405 0.41; Chi²	50 2891 = 105.0	12 874 00, df = 8	50 3214 (P < 0	4.0% 51.3%	2.92 [1.24, 6.87] 2.21 [1.42, 3.45]		
Hao et al 2015 Junaid et al 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	24 1405 0.41; Chi²	50 2891 ² = 105.0 P = 0.00	12 874 00, df = 8	50 3214 (P < 0	4.0% 51.3% .00001); I²	2.92 [1.24, 6.87] 2.21 [1.42, 3.45] = 92%		
Hao et al 2015 Junaid et al 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: Total (95% Cl)	24 1405 0.41; Chi ² Z = 3.49 (I 2603	50 2891 = 105.0 P = 0.00 5047	12 874 00, df = 8 005) 1954	50 3214 (P < 0 5929	4.0% 51.3% .00001); I ² 100.0%	2.92 [1.24, 6.87] 2.21 [1.42, 3.45] = 92% 1.83 [1.39, 2.41]		

Supplementary Figure 5. Forest plot for meta-analysis of the association between the risk of having an infant NSOFC and its association with environmental tobacco smoking sub-grouped according to risk of bias.

6.1.1 Low risk Beaty et al 2001 Little et al 2004 Honein et al 2007 Lie et al 2008 Chevrier et al 2008 Leite and Koifman 2009 Wang et al 2009 Lie tal 2010 Jianyan et al 2010 Mirilas et al 2011 Taghavi et al 2011 Sabbagh et al 2015 Kummet et al 2015 Subtotal (95% CI)	24 67 235 90 97 166 168 59 121 34 113 45 312 :531 ii ² = 62	107 154 1227 334 173 274 586 88 200 35 300 204 4508 8190	Events 18 111 554 106 70 281 192 348 87 25 80 47 2310 4229	Total 130 189 2699 520 167 548 1172 651 200 35 300 244 9626 16481	2.9% 3.8% 4.6% 4.2% 3.8% 4.3% 4.5% 3.6% 0.6% 4.1% 3.7% 4.8%	M-H, Random, 95% CI 1.80 [0.92, 3.53] 0.54 [0.35, 0.83] 0.92 [0.77, 1.09] 1.44 [1.04, 1.99] 1.77 [1.15, 2.72] 1.46 [1.09, 1.96] 2.05 [1.62, 2.60] 1.77 [1.11, 2.84] 1.99 [1.34, 2.96] 13.60 [1.63, 113.25] 1.66 [1.18, 2.35] 1.19 [0.75, 1.88] 1.20 [2.0, 4.41]	2001 2004 2007 2008 2008 2009 2009 2010 2010 2010 2011 2012	M-H, Random, 95% Cl
Beaty et al 2001 Little et al 2004 Honein et al 2007 Lie et al 2008 Chevrier et al 2008 Leite and Koifman 2009 Wang et al 2009 Li et al 2010 Jianyan et al 2010 Mirilas et al 2011 Taghavi et al 2012 Sabbagh et al 2015 Kummet et al 2016 Total events Subtotal (95% CI) Total events 2 Heterogeneity: Tau ² = 0.08; CH Test for overall effect: Z = 3.63 6.1.2 High risk Zhang et al 2010 Jia et al 2011 Li et al 2011 Hao et al 2015 Hoyt et al 2016 Mckinney et al 2016	67 235 90 97 166 168 59 121 34 113 45 312 531 ii ² = 62	154 1227 334 173 274 586 88 200 35 300 204 4508 8190	1111 554 106 70 281 192 348 87 25 80 47 2310 4229	189 2699 520 167 548 1172 651 200 35 300 244 9626	3.8% 4.6% 4.2% 3.8% 4.3% 4.5% 3.6% 3.9% 0.6% 4.1% 3.7% 4.8%	0.54 [0.35, 0.83] 0.92 [0.77, 1.09] 1.44 [1.04, 1.99] 1.77 [1.15, 2.72] 1.46 [1.09, 1.96] 2.05 [1.62, 2.60] 1.77 [1.11, 2.84] 1.99 [1.34, 2.96] 13.60 [1.63, 113.25] 1.66 [1.18, 2.35] 1.19 [0.75, 1.88]	2004 2007 2008 2009 2009 2009 2010 2010 2011 2011	
Little et al 2004 Honein et al 2007 Lie et al 2008 Chevrier et al 2008 Leite and Koifman 2009 Wang et al 2009 Li et al 2010 Jianyan et al 2010 Mirilas et al 2011 Taghavi et al 2012 Sabbagh et al 2015 Kummet et al 2016 10 tal events 2 Heterogeneity: Tau ² = 0.08; Ch Test for overall effect: Z = 3.63 6.1.2 High risk Zhang et al 2010 Jia et al 2011 Li et al 2011 Hao et al 2015 Hoyt et al 2016 Mckinney et al 2016	67 235 90 97 166 168 59 121 34 113 45 312 531 ii ² = 62	154 1227 334 173 274 586 88 200 35 300 204 4508 8190	1111 554 106 70 281 192 348 87 25 80 47 2310 4229	189 2699 520 167 548 1172 651 200 35 300 244 9626	3.8% 4.6% 4.2% 3.8% 4.3% 4.5% 3.6% 3.9% 0.6% 4.1% 3.7% 4.8%	0.54 [0.35, 0.83] 0.92 [0.77, 1.09] 1.44 [1.04, 1.99] 1.77 [1.15, 2.72] 1.46 [1.09, 1.96] 2.05 [1.62, 2.60] 1.77 [1.11, 2.84] 1.99 [1.34, 2.96] 13.60 [1.63, 113.25] 1.66 [1.18, 2.35] 1.19 [0.75, 1.88]	2004 2007 2008 2009 2009 2009 2010 2010 2011 2011	
Honein et al 2007 Lie et al 2008 Chevrier et al 2008 Leite and Kolfman 2009 Wang et al 2009 Li et al 2010 Jianyan et al 2010 Mirilas et al 2011 Taghavi et al 2012 Sabbagh et al 2015 Kummet et al 2016 Total events Li et or overall effect: Z = 3.63 6.1.2 High risk Zhang et al 2010 Jia et al 2011 Li et al 2011 Hao et al 2015 Hoyt et al 2016 Mckinney et al 2016	235 90 97 166 168 59 121 34 113 45 312 2531 $ii^2 = 62$	1227 334 173 274 586 88 200 35 300 204 4508 8190	554 106 70 281 192 348 87 25 80 47 2310 4229	2699 520 167 548 1172 651 200 35 300 244 9626	4.6% 4.2% 3.8% 4.3% 4.5% 3.6% 3.9% 0.6% 4.1% 3.7% 4.8%	0.92 [0.77, 1.09] 1.44 [1.04, 1.99] 1.77 [1.15, 2.72] 1.46 [1.09, 1.96] 2.05 [1.62, 2.60] 1.77 [1.11, 2.84] 1.99 [1.34, 2.96] 13.60 [1.63, 113.25] 1.66 [1.18, 2.35] 1.19 [0.75, 1.88]	2007 2008 2009 2009 2010 2010 2011 2012	
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Li et al 2010 Jianyan et al 2010 Mirilas et al 2011 Taghavi et al 2012 Sabbagh et al 2015 Kummet et al 2016 105 Subtotal (95% CI) Total events 208 Heterogeneity: Tau ² = 0.08; CF Test for overall effect: Z = 3.63 6.1.2 High risk Zhang et al 2010 Jia et al 2011 Li et al 2011 Hao et al 2015 Hoyt et al 2016 Mckinney et al 2016	59 121 34 113 45 312 2531 ii ² = 62	88 200 35 300 204 4508 8190	348 87 25 80 47 2310 4229	651 200 35 300 244 9626	3.6% 3.9% 0.6% 4.1% 3.7% 4.8%	1.77 [1.11, 2.84] 1.99 [1.34, 2.96] 13.60 [1.63, 113.25] 1.66 [1.18, 2.35] 1.19 [0.75, 1.88]	2010 2010 2011 2012	
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Sabbagh et al 2015 Kummet et al 2016 Subtotal (95% CI) Total events 2 Heterogeneity: Tau ² = 0.08; Cf Test for overall effect: Z = 3.63 6.1.2 High risk Zhang et al 2010 Jia et al 2011 Li et al 2011 Hao et al 2015 Hoyt et al 2016 Mckinney et al 2016	45 312 531 ii ² = 62	204 4508 8190	47 2310 4229	244 9626	3.7% 4.8%	1.19 [0.75, 1.88]		
Kummet et al 2016 1 Subtotal (95% Cl) 2 Total events 2 Heterogeneity: Tau ² = 0.08; Cf 2 Test for overall effect: Z = 3.63 3 6.1.2 High risk 2 Zhang et al 2010 Jia et al 2011 Li et al 2011 4 Hao et al 2015 Hoyt et al 2016 Mckinney et al 2016 2	312 531 11 ² = 62	4508 8190	2310 4229	9626	4.8%		2015	
Subtotal (95% CI) 2 Total events 2 Heterogeneity: Tau ² = 0.08; CF 2 Test for overall effect: Z = 3.63 3 6.1.2 High risk 2 Zhang et al 2010 3 Jia et al 2011 1 Li et al 2011 4 Hao et al 2015 40/t5 Hoyt et al 2016 4	2531 ni² = 62	8190 .96, df	4229			1 20 11 20 1 111		
Heterogeneity: Tau ² = 0.08; Cf Test for overall effect: Z = 3.63 6.1.2 High risk Zhang et al 2010 Jia et al 2011 Li et al 2011 Hao et al 2015 Hoyt et al 2016 Mckinney et al 2016	i² = 62				48.7%	1.30 [1.20, 1.41] 1.42 [1.17, 1.71]	2016	•
Test for overall effect: Z = 3.63 6.1.2 High risk Zhang et al 2010 Jia et al 2011 Li et al 2011 Hao et al 2015 Hoyt et al 2016 Mckinney et al 2016								
6.1.2 High risk Zhang et al 2010 Jia et al 2011 Li et al 2011 Hao et al 2015 Hoyt et al 2016 Mckinney et al 2016	(P = 0	.00031	= 12 (P <	< 0.00001); l² = 81%			
Zhang et al 2010 Jia et al 2011 Li et al 2011 Hao et al 2015 Hoyt et al 2016 Mckinney et al 2016								
Jia et al 2011 Li et al 2011 Hao et al 2015 Hoyt et al 2016 Mckinney et al 2016								
Li et al 2011 Hao et al 2015 Hoyt et al 2016 Mckinney et al 2016	224	323	169	454	4.2%	3.82 [2.82, 5.17]	2010	
Hao et al 2015 Hoyt et al 2016 Mckinney et al 2016	402	713	27	221	3.8%	9.29 [6.05, 14.26]	2011	<u></u>
Hoyt et al 2016 Mckinney et al 2016	69	162	54	204	3.7%	2.06 [1.33, 3.20]	2011	
Mckinney et al 2016	285	499	175	480	4.4%	2.32 [1.80, 3.00]	2015	-
	148	1102	369	3324	4.6%	1.24 [1.01, 1.52]		
Dien et al 2017	41	95	20	95	3.0%	2.85 [1.50, 5.39]		
	67	170	43	170	3.7%	1.92 [1.21, 3.05]		
Goveas et al 2017	74	125	53	125	3.5%	1.97 [1.19, 3.26]		
Junaid et al 2017	24	50	12	50	2.3%	2.92 [1.24, 6.87]		
Pi et al 2018	140	240	664	1420	4.3%	1.59 [1.21, 2.10]		
Pi et al 2018 b	56	101	173	561	3.8%	2.79 [1.81, 4.30]		1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Altoe et al 2019	32	150	38	300	3.4%	1.87 [1.11, 3.14]		
Chowchuen et al 2020	14	35	24	70	2.3%	1.28 [0.55, 2.95]		
Sato et al 2021 Subtotal (95% CI)	98	187 3952	46566	94174 101648	4.3% 51.3%	1.13 [0.84, 1.50] 2.23 [1.65, 3.01]	2021	
Total events 1	674		48387					
Heterogeneity: Tau ² = 0.27; Ch Test for overall effect: Z = 5.24			S 633 M	< 0.0000	1); l² = 88	%		
Total (95% CI)	1	2142		118129	100.0%	1.80 [1.51, 2.15]		•
Total events 4	205		52616					
Heterogeneity: Tau ² = 0.17; Ch Test for overall effect: Z = 6.46			•	< 0.0000	1); I² = 88	%	0.01	0.1 1 10 1 <nsofc>NSOFC</nsofc>

Supplementary Figure 6. Forest plot for meta-analysis of the association between maternal environmental tobacco smoking and the risk of having an infant with cleft lip and palate or cleft lip and its association with environmental tobacco smoking after excluding Jia et al, 2011 and Mirilas et al. 2011

	Experim		Con			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
5.1.1 CL/P							
Beaty et al 2001	14	73	18	130	2.2%	1.48 [0.69, 3.18]	
Chevrier et al 2008	65	119	70	167	3.5%	1.67 [1.04, 2.68]	
Chowchuen et al 2020	14	35	24	70	1.9%	1.28 [0.55, 2.95]	
Goveas et al 2017	74	125	53	125	3.3%	1.97 [1.19, 3.26]	
Hao et al 2015	214	362	175	480	4.6%	2.52 [1.90, 3.33]	-
Honein et al 2007	147	699	554	2699	4.9%	1.03 [0.84, 1.27]	+
Hoyt et al 2016	101	740	369	3324	4.8%	1.27 [1.00, 1.60]	-
Jia et al 2011	302	537	27	221		Not estimable	
Jianyan et al 2010	121	200	87	200	3.9%	1.99 [1.34, 2.96]	
Leite and Koifman 2009	124	208	281	548	4.3%	1.40 [1.01, 1.94]	
Lie et al 2008	58	210	106	520	4.0%	1.49 [1.03, 2.16]	
Li et al 2010	59	88	348	651	3.5%	1.77 [1.11, 2.84]	
Little et al 2004	40	76	111	189	3.1%	0.78 [0.46, 1.33]	+
Mckinney et al 2016	41	95	20	95	2.7%	2.85 [1.50, 5.39]	· · · ·
Mirilas et al 2011	34	35	25	35		Not estimable	
Pi et al 2018	131	225	664	1420	4.5%	1.59 [1.19, 2.11]	
Pi et al 2018 b	56	101	173	561	3.7%	2.79 [1.81, 4.30]	
Sabbagh et al 2015	31	151	47	244	3.3%	1.08 [0.65, 1.80]	
Sato et al 2021	82	146	46566	94174	4.3%	1.31 [0.94, 1.82]	
Taghavi et al 2012	113	300	80	300	4.2%	1.66 [1.18, 2.35]	
Zhang et al 2010	175	246	169	454		Not estimable	
Subtotal (95% CI)		3953		105897	66.6%	1.57 [1.33, 1.84]	•
Total events	1485		49746				
Heterogeneity: Tau ² = 0.0		2.38. df =	= 17 (P <	0.0001):	$ ^2 = 68\%$		
Test for overall effect: Z =							
	000000000000000000000000000000000000000	•					
5.1.2 CP							
Beaty et al 2001	10	34	18	133	1.8%	2.66 [1.09, 6.48]	
Chevrier et al 2008	32	54	70	167	2.7%	2.02 [1.08, 3.76]	
Hao et al 2015	71	137	175	480	4.0%	1.87 [1.28, 2.75]	
Honein et al 2007	88	528	554	2699	4.7%	0.77 [0.60, 0.99]	-
Hoyt et al 2016	47	362	369	3324	4.3%	1.19 [0.86, 1.65]	+
Jia et al 2011	100	176	27	221		Not estimable	
Lie et al 2008	32	124	106	520	3.6%	1.36 [0.86, 2.14]	
Little et al 2004	27	42	111	189	2.4%	1.26 [0.63, 2.53]	
Pi et al 2018	9	15	664	1420	1.4%	1.71 [0.60, 4.82]	
Sabbagh et al 2015	14	53	47	244	2.5%	1.50 [0.76, 3.00]	
		41	46566	94174	2.7%	0.65 [0.35, 1.23]	
	16	41				2.95 [1.79, 4.87]	
Sato et al 2021	16 49		169	454	3.3%		
Sato et al 2021 Zhang et al 2010	16 49	77 1467	169	454 103804	3.3% 33.4%		•
Sato et al 2021 Zhang et al 2010 Subtotal (95% CI)	49	77		454 103804		1.44 [1.06, 1.94]	\bullet
Sato et al 2021 Zhang et al 2010 Subtotal (95% CI) Total events	49 395	77 1467	48849	103804	33.4%		•
Sato et al 2021 Zhang et al 2010 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.1	49 395 8; Chi² = 3	77 1467 9.93, df :	48849	103804	33.4%		•
Sato et al 2021 Zhang et al 2010 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z =	49 395 8; Chi² = 3	77 1467 9.93, df = 0.02)	48849	103804 0.0001);	33.4% I² = 75%	1.44 [1.06, 1.94]	•
Sato et al 2021 Zhang et al 2010 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Total (95% CI)	49 395 8; Chi² = 3 2.34 (P = 0	77 1467 9.93, df :	48849 = 10 (P <	103804	33.4% I² = 75%		•
Sato et al 2021 Zhang et al 2010 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Total (95% CI) Total events	49 395 8; Chi ² = 3 2.34 (P = 1 1880	77 1467 9.93, df = 0.02) 5420	48849 = 10 (P < 98595	103804 0.0001); 209701	33.4% ² = 75% 100.0%	1.44 [1.06, 1.94]	•
Sato et al 2021 Zhang et al 2010 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.1 Fest for overall effect: Z = Fotal (95% CI)	49 395 8; Chi ² = 3: 2.34 (P = 1 1880 0; Chi ² = 9	77 1467 9.93, df = 0.02) 5420 7.40, df =	48849 = 10 (P < 98595 = 28 (P <	103804 0.0001); 209701	33.4% ² = 75% 100.0%	1.44 [1.06, 1.94]	◆ ↓ 0.01 0.1 1 10 1

Test for subgroup differences: $Chi^2 = 0.24$, df = 1 (P = 0.62), $I^2 = 0\%$

Supplementary Figure 7. Forest plot for meta-analysis of the association between maternal environmental tobacco smoking and the risk of having an infant with cleft lip and palate or cleft lip and its association with environmental tobacco smoking using the reported adjusted odds ratio.

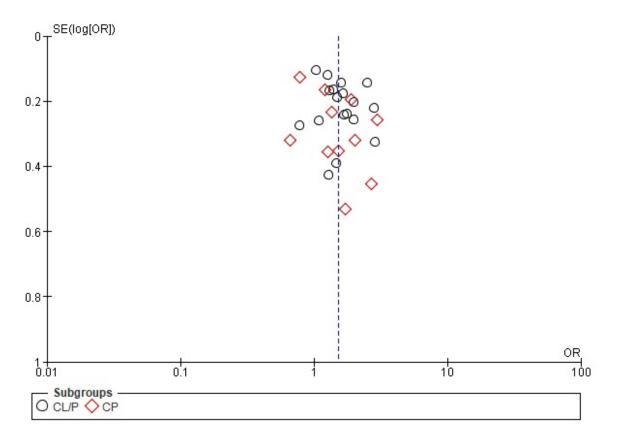
Chudu an Cubanaur	lastOdda Dottal	05	Malakt	Odds Ratio	Veer	Odds Ratio
Study or Subgroup 7.2.1 CL/P	log[Odds Ratio]	SE	weight	IV, Random, 95% CI	rear	IV, Random, 95% CI
			0.001	4 9 4 79 97 4 9 4		
Beaty et al 2001	0.0392		3.9%	1.04 [0.67, 1.61]		
Little et al 2004	-0.1054		3.4%	0.90 [0.53, 1.54]	2004	
Honein et al 2007	0.0306		4.8%	1.03 [0.84, 1.26]		
Lie et al 2008	0.399		4.2%		2008	
Chevrier et al 2008	0.5878		3.4%	1.80 [1.05, 3.07]		
Wang et al 2009	0.7178	0.143	4.6%	2.05 [1.55, 2.71]		
Leite and Koifman 2009	0.3293		4.4%	1.39 [1.01, 1.91]		· · · · · · · · · · · · · · · · · · ·
Li et al 2010	0.6931		3.5%	2.00 [1.20, 3.33]		
Jianyan et al 2010	0.6878		4.1%	1.99 [1.34, 2.96]		
Jia et al 2011	2.2225		3.9%	9.23 [5.96, 14.30]		
Mirilas et al 2011	0.5933	0.492	2.0%	1.81 [0.69, 4.75]	2011	
Taghavi et al 2012	-0.4894	0.1809	4.2%	0.61 [0.43, 0.87]	2012	
Sabbagh et al 2015	-0.1474	0.2612	3.5%	0.86 [0.52, 1.44]	2015	•
Hao et al 2015	0.9243	0.1429	4.6%	2.52 [1.90, 3.33]	2015	
Kummet et al 2016	0.1044	0.0584	5.1%	1.11 [0.99, 1.24]	2016	
Hoyt et al 2016	0.2357	0.1205	4.7%	1.27 [1.00, 1.60]	2016	
Subtotal (95% CI)			64.3%	1.52 [1.18, 1.95]		•
Heterogeneity: Tau ² = 0.2	2; Chi ² = 152.95, df	= 15 (P	< 0.00001); I ² = 90%		
Test for overall effect: Z =	: 3.25 (P = 0.001)					
7.2.2 CP						
Beaty et al 2001	0.157	0.2769	3.4%	1.17 [0.68, 2.01]	2001	
Little et al 2004	0.0953	0.4023	2.5%	1.10 [0.50, 2.42]	2004	
Honein et al 2007	0.0953	0.1625	4.4%	1.10 [0.80, 1.51]	2007	
Chevrier et al 2008	0.7706	0.3172	3.1%		2008	
Lie et al 2008	0.0488	0.3299	3.0%	1.05 [0.55, 2.00]	2008	
Leite and Koifman 2009	0.5128	0.3154	3.1%		2009	
Hao et al 2015	0.6286	0.1955	4.1%	1.87 [1.28, 2.75]	2015	
Sabbagh et al 2015	0.4086	0.3513	2.8%	1.50 [0.76, 3.00]		
Kummet et al 2016	0.1655		5.0%	1.18 [1.00, 1.39]		-
Hoyt et al 2016	0.178		4.4%	1.19 [0.86, 1.65]		
Subtotal (95% CI)			35.7%	1.28 [1.12, 1.46]		◆
Heterogeneity: Tau ² = 0.0	0: Chi ² = 9.98, df = 9	P = 0	$(35): ^2 = 10$	1751 (Sil) (Sil)		2
Test for overall effect: Z =	같아요. 전화가장 이 같아요. 한 것이라. 한 것이 같아요. 한 것이 같아요. 한 것이 같아요. 한 것이 없는 것이 같아요. 한 것이 없는 것이 없 않는 것이 없는 것이 않는 것이 않는 것이 없는 것이 않는 것이 없는 것이 않는 것이 없는 것이 않는 것이 않는 것이 않는 것이 없는 것이 없는 것이 않는 것이 않이		<i>n</i> · · · ·	228		
Total (95% CI)			100.0%	1.45 [1.22, 1.72]		•
Heterogeneity: Tau ² = 0.1	5; Chi ² = 163.46. df	= 25 (P	< 0.00001); l ² = 85%		
Test for overall effect: Z =		, v				0.1 0.2 0.5 1 2 5 10 <nsofc>NSOFC</nsofc>

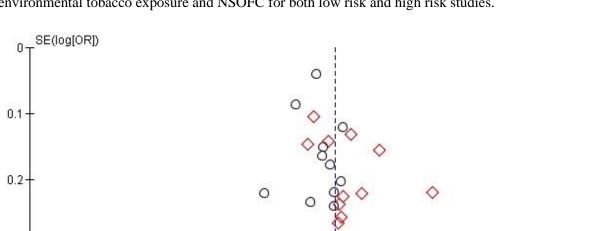
Supplementary Figure 8. Forest plot for meta-analysis of the association between maternal environmental tobacco smoking and the risk of having an infant with NSOFC according to period of

exposure

	NSO	steen st	Cont			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
5.4.1 First trimester pe	riod						
Little et al 2004	67	154	111	189	5.5%	0.54 [0.35, 0.83]	
Sato et al 2021	98	187	46566	94174	6.2%	1.13 [0.84, 1.50]	- -
Kummet et al 2016	1312	4508	2310	9626	6.9%	1.30 [1.20, 1.41]	•
Lie et al 2008	90	334	106	520	6.1%	1.44 [1.04, 1.99]	-
Chevrier et al 2008	97	173	70	167	5.5%	1.77 [1.15, 2.72]	
Beaty et al 2001	24	107	18	130	4.2%	1.80 [0.92, 3.53]	
Altoe et al 2019	32	150	38	300	5.0%	1.87 [1.11, 3.14]	
Jia et al 2011	402	713	27	221	5.5%	9.29 [6.05, 14.26]	· · ·
Subtotal (95% CI)		6326		105327	44.8%	1.66 [1.09, 2.53]	•
Total events	2122		49246				
Heterogeneity: Tau ² = 0.	32; Chi ² =	101.77,	df = 7 (P	< 0.0000	1); l ² = 93	%	
Test for overall effect: Z	= 2.36 (P =	= 0.02)					
5.4.2 Pregestation and	First trim	ester pe	riods				
Honein et al 2007	235	1227	554	2699	6.7%	0.92 [0.77, 1.09]	-
Sabbagh et al 2015	45	204	47	244	5.3%	1.19 [0.75, 1.88]	
Hoyt et al 2016	148	1102	369	3324	6.6%	1.24 [1.01, 1.52]	-
Chowchuen et al 2020	14	35	24	70	3.4%	1.28 [0.55, 2.95]	2
Li et al 2010	59	88	348	651	5.2%	1.77 [1.11, 2.84]	
Dien et al 2017	67	170	43	170	5.3%	1.92 [1.21, 3.05]	
Jianyan et al 2010	121	200	87	200	5.7%	1.99 [1.34, 2.96]	
Li et al 2011	69	162	54	204	5.4%	2.06 [1.33, 3.20]	
Hao et al 2015	285	499	175	480	6.4%	2.32 [1.80, 3.00]	-
Mckinney et al 2016	41	95	20	95	4.3%	2.85 [1.50, 5.39]	
Mirilas et al 2011	34	35	25	35	0.9%	13.60 [1.63, 113.25]	
Subtotal (95% CI)		3817		8172	55.2%	1.69 [1.28, 2.22]	◆
Total events	1118		1746				
Heterogeneity: Tau ² = 0.	15; Chi ² =	58.25, c	lf = 10 (P	< 0.0000	1); l ² = 83	%	
Test for overall effect: Z	= 3.71 (P =	= 0.0002	2)				
Total (95% CI)		10143		113499	100.0%	1.67 [1.35, 2.07]	•
Total events	3240		50992				
Heterogeneity: Tau ² = 0.	17; Chi ² =	159.95,	df = 18 (P < 0.000	01); l ² = 8	9%	0.01 0.1 1 10
Test for overall effect: Z	= 4.68 (P ·	< 0.0000)1)				<pre></pre>

Supplementary Figure 9. Funnel plot for studies showing the relationship between maternal environmental tobacco exposure and both CL/P and CP.





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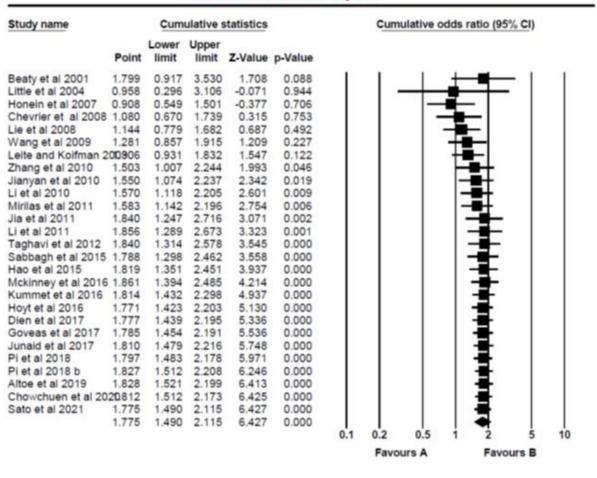
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🔷 High risk

Supplementary Figure 10. Funnel plot for studies showing the relationship between maternal environmental tobacco exposure and NSOFC for both low risk and high risk studies.

Supplementary Figure 11. Cumulative meta-analysis for the stability of evidence from 2011

through 2021.



Cumulative Meta Analysis

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