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**Article:**

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## Supplementary material

Online table 1. Search strategy for review of research on reproductive effects of caffeine.

### MEDLINE and EMBASE

1. exp cohort studies/
2. cohort\$.tw.
3. exp case-control studies/
4. case-control\$.tw.
5. epidemiologic methods/
6. or/1-5
7. (animals not (humans and animals)).sh.
8. 6 not 7
9. exp caffeine/
10. caffein\$.ab,ti.
11. 1,3,7-trimethylxanthine.ab,ti.
12. 137-trimethylxanthine.ab,ti.
13. paraxanthine.ab,ti.
14. coffee.ab,ti.
15. or/9-14
16. ((f?etal or f?etus or intrauterine) adj2 (growth or restriction or retardation)).tw.
17. FGR.ab,ti.
18. IUGR.ab,ti.
19. (small adj2 gestation\$).tw.
20. SGA.ab,ti.
21. exp birth weight/
22. birth weight.tw.
23. exp miscarriage/
24. miscarriage.tw.
25. exp spontaneous abortion/
26. spontaneous abortion.tw.
27. exp preterm birth/
28. ((preterm or pre-term) adj2 (birth or delivery)).tw.
29. or/16-28
30. adverse effect\$.tw.
31. pregnancy.tw.
32. and/30-31
33. 29 or 32
34. 6 and 15 and 33

Online table 2a. Characteristics and risk of bias table for publications included in meta-analysis of caffeine and miscarriage.

Authors	Location	Design	Source of caffeine	Adjustments						Risk of bias <sup>a</sup>		
				age	parity	previous history	smoking	alcohol	socio-economic	selection	comparability	exposure /outcome
Srisuphan et al. 1986[1]	US	cohort	all							****		***
Hansteen et al. 1990[2]	Norway	case-control	coffee	✓						**	*	*
Wilcox et al. 1990[3]	US	cohort	all							****		***
Fenster et al. 1991[4]	US	case-control	all	✓		✓	✓	✓	✓	***	**	*
Kline et al. 1991[5]	US	case-control	all	✓					✓	***	*	*
Armstrong et al. 1992[6]	US	case-control	coffee	✓	✓	✓			✓	***	*	*
Infante-Rivard et al. 1993[7]	US	case-control	all	✓		✓	✓	✓	✓	***	**	*
Mills et al. 1993[8]	US	cohort	all							***		***
Dominguez-Rojas et al. 1994[9]	Spain	cohort	coffee	✓		✓				**	*	***
Dlugosz et al. 1996[10]	US	cohort	all	✓	✓	✓	✓	✓	✓	****	**	***
Agnesi et al. 1997[11]	Italy	case-control	coffee	✓		✓				**	*	*
Fenster et al. 1997[12]	US	cohort	all	✓	✓	✓	✓	✓	✓	****	**	***
Parazzini et al. 1998[13]	Italy	case-control	coffee	✓	✓	✓	✓	✓	✓	**	**	
Cnattingius et al. 2000[14]	Sweden	case-control	all	✓	✓	✓	✓	✓	✓	***	**	*
Wen et al. 2001[15]	US	cohort	all							***		**
Giannelli et al. 2003[16]	UK	case-control	all	✓	✓					***	*	*
Rasch et al. 2003[17]	Denmark	case-control	all	✓	✓		✓	✓	✓	***	**	**
Tolstrup et al. 2003[18]	Denmark	cohort	all	✓	✓	✓	✓	✓	✓	****	**	***
Wisborg et al. 2003[19]	Denmark	cohort	coffee							***		***
Khoury et al. 2004[20]	US	cohort	all	✓		✓	✓			***	**	***
Bech et al. 2005[21]	Denmark	cohort	coffee	✓	✓		✓	✓	✓	***	**	***
George et al. 2006[22]	Sweden	case-control	all	✓	✓	✓	✓	✓		***	**	*
Maconochie et al. 2007[23]	UK	case-control	all	✓		✓				***	*	*
Savitz et al. 2008[24]	US	cohort	all	✓	✓	✓		✓	✓	***	*	**
Weng et al. 2008[25]	US	cohort	all	✓		✓	✓	✓	✓	****	**	***
Greenwood et al. 2010[26]	UK	cohort	all	✓	✓		✓	✓		****	**	***

<sup>a</sup> Risk of bias based on Newcastle-Ottawa quality assessment scale for case-control or cohort studies, as appropriate.

Online table 2b. Characteristics and risk of bias table for publications included in meta-analysis of caffeine and stillbirth.

Authors	Location	Design	Source of caffeine	Adjustments						Risk of bias <sup>a</sup>		
				age	parity	previous history	smoking	alcohol	socio-economic	selection	comparability	exposure /outcome
Linn et al. 1982[27]	US	case-control	coffee							****		*
Wisborg et al. 2003[28]	Denmark	cohort	coffee	✓	✓		✓	✓	✓	***	**	***
Bech et al. 2005[21]	Denmark	cohort	coffee	✓	✓		✓	✓	✓	***	**	***
Matijasevich et al. 2006[29]	Uruguay	case-control	all			✓	✓		✓	****	*	*
Greenwood et al. 2010[26]	UK	cohort	all	✓	✓		✓	✓		****	**	***

<sup>a</sup> Risk of bias based on Newcastle-Ottawa quality assessment scale for case-control or cohort studies, as appropriate.

Online table 2c. Characteristics and risk of bias table for publications included in meta-analysis of caffeine and preterm delivery.

Authors	Location	Design	Source of caffeine	Adjustments						Risk of bias <sup>a</sup>		
				age	parity	previous history	smoking	alcohol	socio-economic	selection	comparability	exposure /outcome
Berkowitz et al. 1982[30]	US	case-control	coffee							***		*
Olsen et al. 1991[31]	Denmark	cohort	coffee		✓		✓	✓	✓	***	*	***
McDonald et al. 1992[32]	US	cohort	coffee	✓		✓	✓	✓	✓	**	**	***
Williams et al. 1992[33]	US	case-control	coffee	✓	✓	✓	✓	✓	✓	****	**	*
Fortier et al. 1993[34]	US	case-control	all		✓	✓	✓		✓	***	*	*
Pastore et al. 1995[35]	US	case-control	all		✓		✓	✓		***	*	**
Peacock et al. 1995[36]	UK	cohort	all							****		***
Bicalho et al. 2002[37]	US	case-control	all	✓	✓	✓	✓		✓	**	**	*
Bracken et al. 2003[38]	US	cohort	all	✓	✓		✓		✓	****	**	***
Khoury et al. 2004[20]	US	cohort	all	✓		✓	✓			***	**	***
de Souza et al. 2005[39]	US	case-control	all							***		*
Chiaffarino et al. 2006[40]	Italy	case-control	all	✓	✓	✓	✓		✓	****	**	*
Boylan et al. 2008[41]	UK	cohort	all	✓		✓	✓	✓		****	**	***
Bakker et al. 2010[42]	Netherlands	cohort	all	✓	✓		✓	✓	✓	****	**	***
Sengpiel et al. 2013[43]	Norway	cohort	all	✓	✓	✓	✓	✓	✓	***	**	***

<sup>a</sup> Risk of bias based on Newcastle-Ottawa quality assessment scale for case-control or cohort studies, as appropriate.

Online table 2d. Characteristics and risk of bias table for publications included in meta-analysis of caffeine and low birth weight.

Authors	Location	Design	Source of caffeine	Adjustments						Risk of bias <sup>a</sup>		
				age	parity	previous history	smoking	alcohol	socio-economic	selection	comparability	exposure /outcome
Linn et al. 1982[27]	US	case-control	coffee							****		*
Martin et al. 1987[44]	US	cohort	all		✓		✓			****	*	***
Caan et al. 1989[45]	US	case-control	all		✓		✓	✓		**	*	*
Fenster et al. 1991[46]	US	case-control	all	✓	✓		✓	✓		***	**	*
Olsen et al. 1991[31]	Denmark	cohort	coffee		✓		✓	✓	✓	***	*	***
McDonald et al. 1992[32]	US	cohort	coffee	✓		✓	✓	✓	✓	**	**	***
Santos et al. 1998[47]	Brazil	case-control	all				✓		✓	**	*	*
Bicalho et al. 2002[37]	US	case-control	all	✓	✓	✓	✓		✓	**	**	*
Bracken et al. 2003[38]	US	cohort	all	✓	✓		✓		✓	****	**	***
Boylan et al. 2008[41]	UK	cohort	all	✓	✓		✓	✓		****	**	***
Bakker et al. 2010[42]	Netherlands	cohort	all	✓	✓		✓	✓	✓	****	**	***

<sup>a</sup> Risk of bias based on Newcastle-Ottawa quality assessment scale for case-control or cohort studies, as appropriate.

Online table 2e. Characteristics and risk of bias table for publications included in meta-analysis of caffeine and small for gestational age infants.

Authors	Location	Design	Source of caffeine	Adjustments						Risk of bias <sup>a</sup>			
				age	parity	previous history	smoking	alcohol	socio-economic	selection	comparability	exposure /outcome	
Fenster et al. 1991[46]	US	case-control	all				✓	✓			***	*	*
McDonald et al. 1992[32]	US	cohort	coffee	✓		✓	✓	✓	✓		**	**	***
Fortier et al. 1993[34]	US	case-control	all	✓	✓	✓	✓		✓		***	**	*
Mills et al. 1993[8]	US	cohort	all								***		***
Rondo et al. 1996[48]	US	case-control	coffee				✓	✓	✓		***	*	*
Grosso et al. 2001[49]	US	cohort	all		✓		✓				****	*	***
Bicalho et al. 2002[37]	US	case-control	all	✓	✓	✓	✓		✓		**	**	*
Bracken et al. 2003[38]	US	cohort	all	✓	✓		✓		✓		****	**	***
Vik et al. 2003[50]	Norway	cohort	all								***		***
Parazzini et al. 2005[51]	Italy	case-control	coffee	✓	✓	✓	✓		✓		***	**	*
Xue et al. 2007[52]	US	cohort	coffee		✓		✓		✓		**	*	**
Boylan et al. 2008[41]	UK	cohort	all	✓	✓		✓	✓			****	**	***
Bakker et al. 2010[42]	Netherlands	cohort	all	✓	✓		✓	✓	✓		****	**	***
Sengpiel et al. 2013[43]	Norway	cohort	all	✓	✓	✓	✓	✓	✓		***	**	***
van den Berg et al. 2013[53]	Netherlands	cohort	all						✓		****		***

<sup>a</sup> Risk of bias based on Newcastle-Ottawa quality assessment scale for case-control or cohort studies, as appropriate.



Online table 3a. Subgroup analyses for caffeine intake during pregnancy and incidence of miscarriage.

Subgroup		RR (95% CI)	I <sup>2</sup>	n	P <sub>het</sub> <sup>a</sup>	P <sub>het</sub> <sup>b</sup>
study design	prospective	1.08 (1.04, 1.13)	46%	13	0.03	
	retrospective	1.12 (1.07, 1.17)	88%	12	<0.001	0.6
caffeine from coffee only	yes	1.10 (1.04, 1.17)	92%	6	<0.001	
	no	1.11 (1.07, 1.15)	60%	19	<0.001	0.7
geographic location	EU	1.11 (1.06, 1.16)	83%	12	<0.001	
	Americas	1.11 (1.05, 1.16)	72%	13	<0.001	
	Other			0		0.9
adjusted for maternal age	yes	1.10 (1.06, 1.14)	82%	20	<0.001	
	no	1.13 (1.07, 1.20)	0%	5	0.6	0.4
adjusted for ethnic group	yes	1.06 (0.99, 1.13)	62%	6	0.02	
	no	1.13 (1.08, 1.17)	78%	19	<0.001	0.2
adjusted for socio-economic factors	yes	1.11 (1.06, 1.15)	87%	13	<0.001	
	no	1.10 (1.05, 1.16)	49%	12	0.03	0.8
adjusted for parity	yes	1.10 (1.05, 1.15)	86%	12	<0.001	
	no	1.11 (1.06, 1.16)	65%	13	<0.001	0.6
adjusted for previous pregnancy outcome	yes	1.11 (1.06, 1.17)	85%	14	<0.001	
	no	1.09 (1.05, 1.14)	58%	11	0.008	0.8
adjusted for smoking	yes	1.15 (1.08, 1.22)	82%	13	<0.001	
	no	1.06 (1.03, 1.09)	65%	12	<0.001	0.1
adjusted for alcohol	yes	1.13 (1.06, 1.19)	83%	13	<0.001	
	no	1.07 (1.03, 1.10)	66%	12	<0.001	0.5
adjusted for nausea	yes	1.13 (1.01, 1.27)	90%	6	<0.001	
	no	1.08 (1.05, 1.12)	69%	19	<0.001	0.7
adjusted for gestational age	yes	1.13 (1.06, 1.21)	41%	6	0.1	
	no	1.10 (1.06, 1.13)	82%	19	<0.001	0.5

<sup>a</sup> P for heterogeneity within each subgroup. <sup>b</sup> P for heterogeneity between each subgroup

Online table 3b. Subgroup analyses for caffeine intake during pregnancy and incidence of stillbirth.

Subgroup		RR (95% CI)	I <sup>2</sup>	n	P <sub>het</sub> <sup>a</sup>	P <sub>het</sub> <sup>b</sup>
study design	prospective	1.18 (1.00, 1.40)	87%	3	<0.001	
	retrospective	1.21 (1.00, 1.48)	64%	2	.09	0.9
caffeine from coffee only	yes	1.07 (1.01, 1.13)	0%	3	.6	
	no	1.41 (1.22, 1.62)	48%	2	.2	0.02
geographic location	EU	1.18 (1.00, 1.40)	87%	3	<0.001	
	Americas	1.08 (0.88, 1.32)		1		
	Other	1.32 (1.17, 1.49)		1		0.8
adjusted for maternal age	yes	1.18 (1.00, 1.40)	87%	3	<0.001	
	no	1.21 (1.00, 1.48)	64%	2	.09	0.9
adjusted for ethnic group	yes			0		
	no	1.19 (1.05, 1.35)	82%	5	<0.001	
adjusted for socio-economic factors	yes	1.14 (1.00, 1.29)	80%	3	.006	
	no	1.29 (0.91, 1.83)	85%	2	.01	0.5
adjusted for parity	yes	1.18 (1.00, 1.40)	87%	3	<0.001	
	no	1.21 (1.00, 1.48)	64%	2	.09	0.9
adjusted for previous adverse pregnancy outcome	yes	1.32 (1.17, 1.49)		1		
	no	1.16 (1.01, 1.33)	81%	4	.001	0.6
adjusted for smoking	yes	1.21 (1.05, 1.40)	86%	4	<0.001	
	no	1.08 (0.88, 1.32)		1		0.6
adjusted for alcohol	yes	1.18 (1.00, 1.40)	87%	3	<0.001	
	no	1.21 (1.00, 1.48)	64%	2	.09	0.9
adjusted for nausea	yes	1.32 (1.17, 1.49)		1		
	no	1.16 (1.01, 1.33)	81%	4	.001	0.6
adjusted for gestational age	yes			0		
	no	1.19 (1.05, 1.35)	82%	5	<0.001	

<sup>a</sup> P for heterogeneity within each subgroup. <sup>b</sup> P for heterogeneity between each subgroup

Online table 3c. Subgroup analyses for caffeine intake during pregnancy and incidence of preterm birth.

Subgroup		RR (95% CI)	I <sup>2</sup>	n	P <sub>het</sub> <sup>a</sup>	P <sub>het</sub> <sup>b</sup>
study design	prospective	1.04 (1.00, 1.08)	65%	9	.004	
	retrospective	0.93 (0.86, 1.01)	27%	6	.2	0.04
caffeine from coffee only	yes	1.04 (0.99, 1.09)	75%	4	.007	
	no	1.00 (0.94, 1.06)	58%	11	.008	0.4
geographic location	EU	1.02 (0.98, 1.05)	17%	6	.3	
	Americas	1.01 (0.94, 1.09)	75%	9	<0.001	
	Other			0		1
adjusted for maternal age	yes	1.03 (0.97, 1.09)	75%	9	<0.001	
	no	1.00 (0.96, 1.04)	4%	6	.4	0.4
adjusted for ethnic group	yes	1.01 (0.94, 1.09)	81%	6	<0.001	
	no	1.01 (0.97, 1.06)	29%	9	.2	1
adjusted for socio-economic factors	yes	1.02 (0.97, 1.06)	70%	9	<0.001	
	no	1.03 (0.92, 1.14)	57%	6	.04	0.9
adjusted for parity	yes	1.00 (0.95, 1.06)	72%	9	<0.001	
	no	1.04 (0.97, 1.11)	45%	6	.1	0.5
adjusted for previous adverse pregnancy outcome	yes	1.02 (0.96, 1.08)	77%	8	<0.001	
	no	1.01 (0.96, 1.06)	25%	7	.2	0.9
adjusted for smoking	yes	1.02 (0.98, 1.06)	69%	12	<0.001	
	no	0.97 (0.88, 1.07)	0%	3	.4	0.7
adjusted for alcohol	yes	1.03 (0.99, 1.07)	69%	7	.004	
	no	0.99 (0.89, 1.10)	57%	8	.02	0.4
adjusted for nausea	yes	0.98 (0.92, 1.05)		1		
	no	1.02 (0.98, 1.06)	64%	14	<0.001	0.7
adjusted for gestational age	yes	1.01 (0.93, 1.11)		1		
	no	1.02 (0.97, 1.06)	66%	14	<0.001	1

<sup>a</sup> P for heterogeneity within each subgroup. <sup>b</sup> P for heterogeneity between each subgroup

Online table 3d. Subgroup analyses for caffeine intake during pregnancy and incidence of low birth weight.

Subgroup		RR (95% CI)	I <sup>2</sup>	n	P <sub>het</sub> <sup>a</sup>	P <sub>het</sub> <sup>b</sup>
study design	prospective	1.10 (1.03, 1.17)	77%	6	<0.001	
	retrospective	1.02 (0.91, 1.16)	78%	5	.001	0.3
caffeine from coffee only	yes	1.04 (1.01, 1.07)	52%	3	.1	
	no	1.12 (0.98, 1.28)	80%	8	<0.001	0.6
geographic location	EU	1.08 (1.01, 1.16)	45%	3	.2	
	Americas	1.09 (1.01, 1.19)	81%	7	<0.001	
	Other	0.92 (0.81, 1.04)		1		0.5
adjusted for maternal age	yes	1.06 (0.97, 1.15)	67%	6	.009	
	no	1.10 (1.00, 1.20)	81%	5	<0.001	0.7
adjusted for ethnic group	yes	1.08 (0.98, 1.18)	79%	8	<0.001	
	no	1.07 (1.02, 1.12)	43%	3	.2	0.8
adjusted for socio-economic factors	yes	1.02 (0.97, 1.07)	64%	6	.02	
	no	1.24 (1.07, 1.43)	71%	5	.008	0.02
adjusted for parity	yes	1.13 (1.02, 1.25)	76%	8	<0.001	
	no	1.03 (0.97, 1.09)	73%	3	.03	0.3
adjusted for previous adverse pregnancy outcome	yes	0.95 (0.80, 1.13)	85%	2	.01	
	no	1.11 (1.04, 1.19)	69%	9	.001	0.1
adjusted for smoking	yes	1.07 (1.01, 1.14)	76%	10	<0.001	
	no	1.08 (1.03, 1.13)		1		0.9
adjusted for alcohol	yes	1.06 (1.02, 1.11)	51%	6	.07	
	no	1.06 (0.91, 1.23)	87%	5	<0.001	0.5
adjusted for nausea	yes			0		
	no	1.07 (1.01, 1.12)	75%	11	<0.001	
adjusted for gestational age	yes	1.24 (1.03, 1.49)	76%	3	.01	
	no	1.03 (0.98, 1.08)	67%	8	.003	0.1

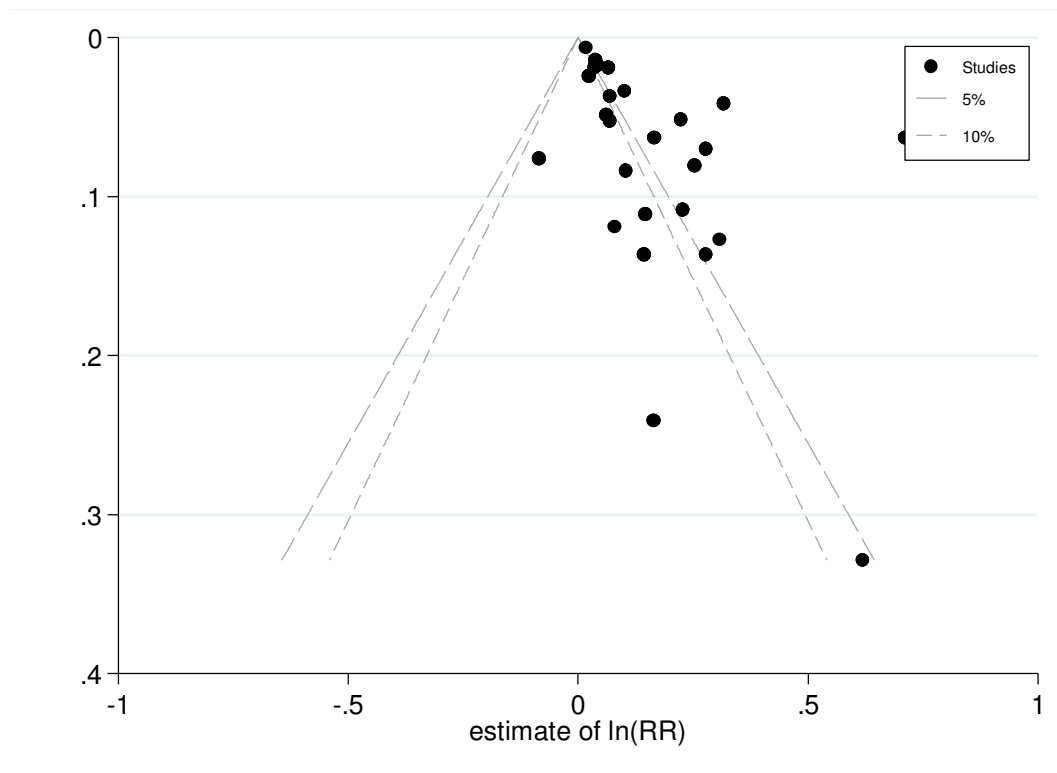
<sup>a</sup> P for heterogeneity within each subgroup. <sup>b</sup> P for heterogeneity between each subgroup

Online table 3e. Subgroup analyses for caffeine intake during pregnancy and incidence of small for gestational age infants.

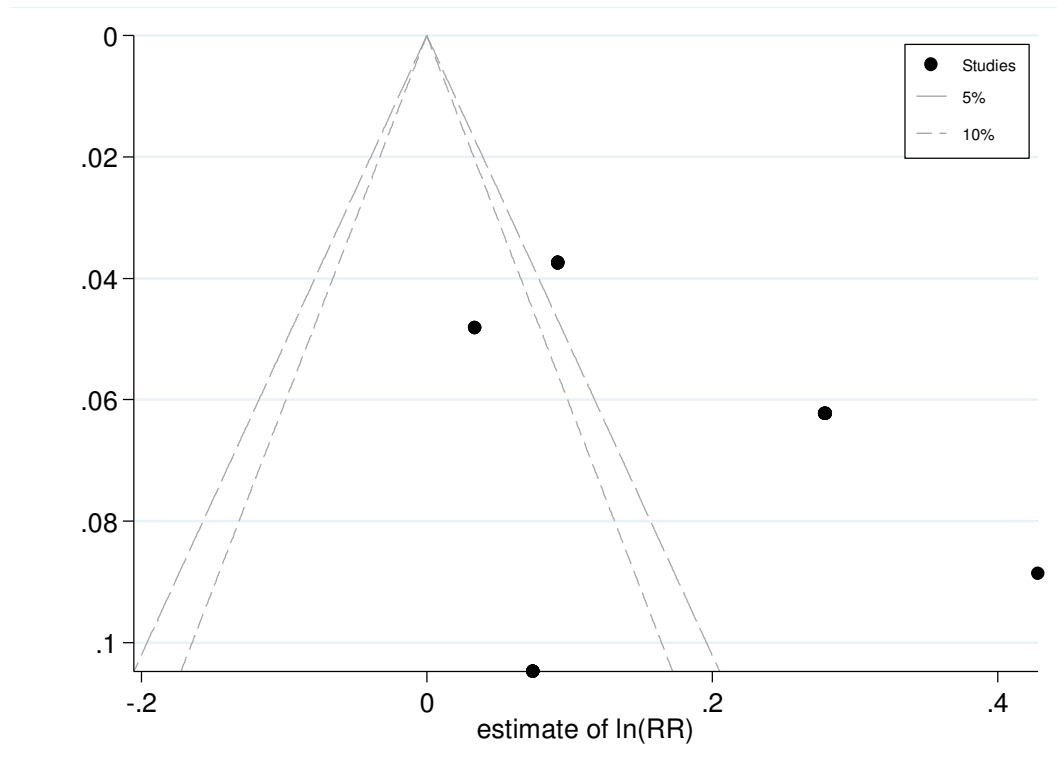
Subgroup		RR (95% CI)	I <sup>2</sup>	n	P <sub>het</sub> <sup>a</sup>	P <sub>het</sub> <sup>b</sup>
study design	prospective	1.11 (1.05, 1.16)	70%	9	<0.001	
	retrospective	1.09 (1.03, 1.16)	52%	6	.06	0.7
caffeine from coffee only	yes	1.05 (0.99, 1.10)	42%	3	.2	
	no	1.13 (1.07, 1.19)	58%	11	.008	0.2
geographic location	EU	1.11 (1.05, 1.16)	52%	6	.06	
	Americas	1.09 (1.04, 1.16)	70%	9	<0.001	
	Other			0		0.8
adjusted for maternal age	yes	1.07 (1.03, 1.11)	51%	8	.05	
	no	1.17 (1.08, 1.28)	64%	7	.01	0.2
adjusted for ethnic group	yes	1.08 (1.01, 1.15)	61%	5	.04	
	no	1.11 (1.06, 1.17)	60%	10	.007	0.5
adjusted for socio-economic factors	yes	1.08 (1.05, 1.11)	55%	10	.02	
	no	1.21 (1.05, 1.40)	68%	5	.01	0.1
adjusted for parity	yes	1.08 (1.05, 1.11)	28%	9	.2	
	no	1.21 (1.08, 1.36)	80%	6	<0.001	0.2
adjusted for previous adverse pregnancy outcome	yes	1.05 (1.02, 1.09)	51%	5	.08	
	no	1.15 (1.09, 1.21)	48%	10	.05	0.04
adjusted for smoking	yes	1.08 (1.05, 1.11)	53%	12	.02	
	no	1.31 (1.09, 1.58)	67%	3	.05	0.05
adjusted for alcohol	yes	1.09 (1.04, 1.14)	63%	6	.02	
	no	1.10 (1.03, 1.18)	63%	9	.005	0.9
adjusted for nausea	yes	1.07 (1.04, 1.11)		1		
	no	1.11 (1.06, 1.15)	67%	14	<0.001	0.7
adjusted for gestational age	yes	1.14 (1.07, 1.21)	0%	2	.8	
	no	1.09 (1.05, 1.13)	66%	13	<0.001	0.5

<sup>a</sup> P for heterogeneity within each subgroup. <sup>b</sup> P for heterogeneity between each subgroup

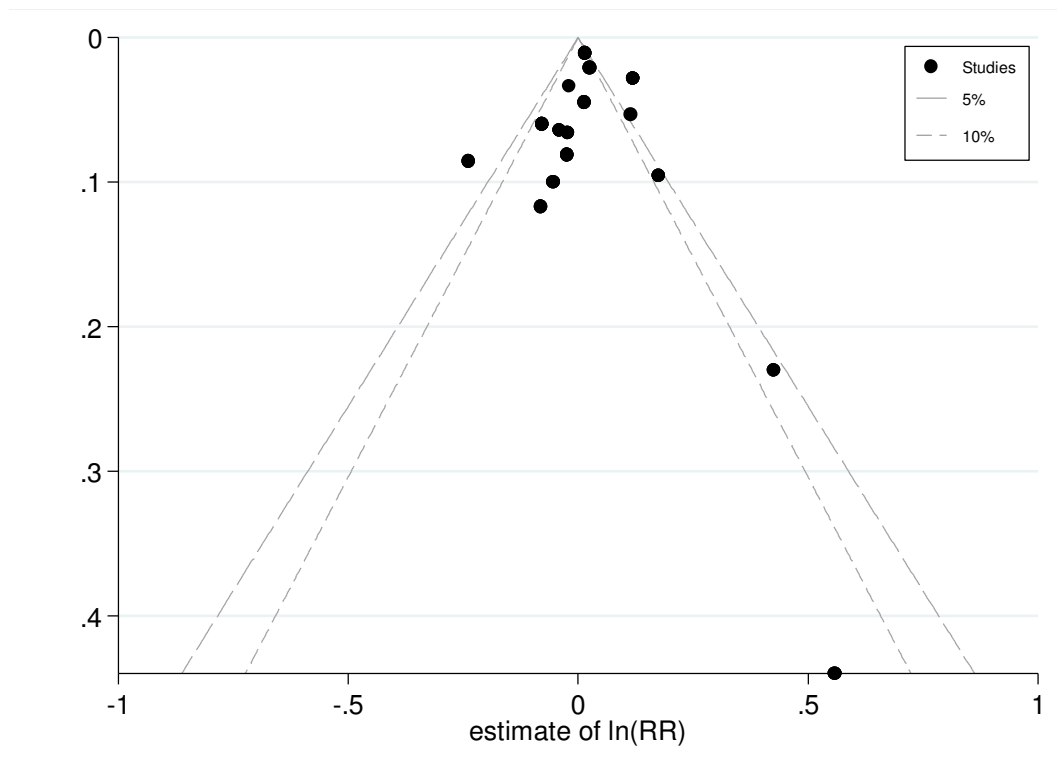
Online figure 1a. Contour-enhanced funnel plot for caffeine intake during pregnancy and incidence of miscarriage.



Online figure 1b. Contour-enhanced funnel plot for caffeine intake during pregnancy and incidence of stillbirth.

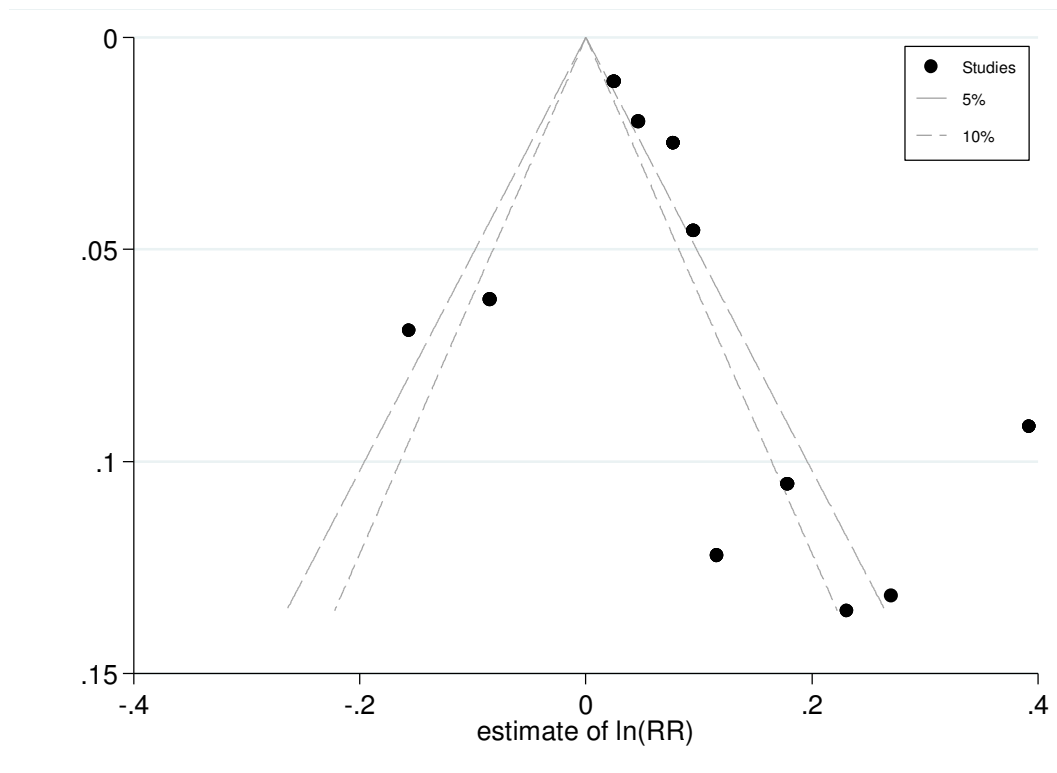


Online figure 1c. Contour-enhanced funnel plot for caffeine intake during pregnancy and incidence of preterm birth.

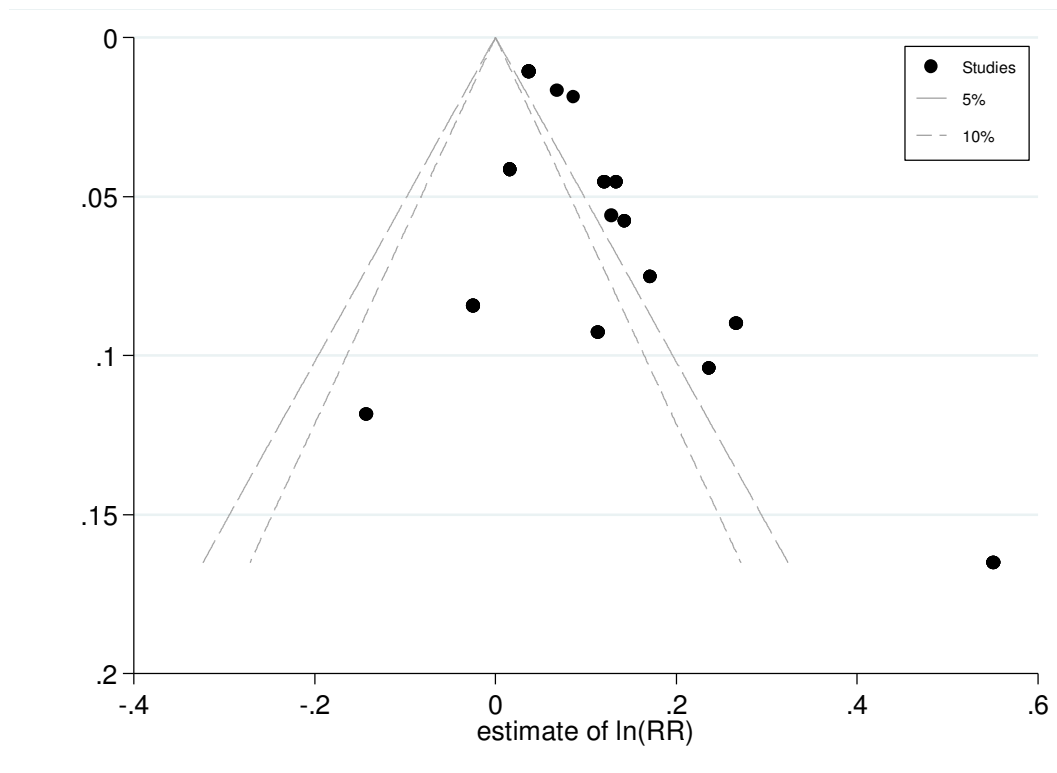




Online figure 1d. Contour-enhanced funnel plot for caffeine intake during pregnancy and incidence of low birth weight.



Online figure 1e. Contour-enhanced funnel plot for caffeine intake during pregnancy and incidence of small for gestational age infants.



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