Supplementary Material

Efficacy of Low-Dose Estrogen–Progestins and Progestins in Japanese Women with Dysmenorrhea: A Systematic Review and Network Meta-analysis

Author Details

Masaru Iwata[1], Yoshihiro Oikawa[1], Yutaka Shimizu[1], Naotaka Sakashita[2], Ayako Shoji[2,3], Ataru Igarashi[3,4], Yutaka Osuga[5]

[1] Mochida Pharmaceutical Co., Ltd., Tokyo, Japan

[2] Medilead, Inc., Tokyo, Japan

[3] Department of Health Economics and Outcomes Research, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan

[4] Unit of Public Health and Preventive Medicine, Yokohama City University School of Medicine, Kanagawa, Japan

[5] Department of Obstetrics and Gynecology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Corresponding author

Masaru Iwata

Mochida Pharmaceutical Co., Ltd., Tokyo, Japan

e-mail address: masaru.iwata@mochida.co.jp

Table S1: Search Strategy in MEDLINE via PubMed

Search number	Query	Results
#1	dysmenorrhea [MeSH Terms] OR dysmenorrhea [tiab]	6,890
#2	"primary dysmenorrhea" [tiab] OR "functional dysmenorrhea" [tiab] OR "organic dysmenorrhea" [tiab] OR "secondary dysmenorrhea" [tiab]	1,174
#3	#1 OR #2	6,890
#4	Gestagen [tiab] OR progesterone [tiab] OR Progestin [tiab] OR Progestogen [tiab] OR Estrogen [tiab] OR Oestrogen [tiab] OR Dydrogesterone [tiab] OR Duphaston [tiab] OR "Chlormadinone-Acetate" [tiab] OR Lutoral [tiab] OR Norgestrel [tiab] OR Ethinylestradiol [tiab] OR PLANOVAR [tiab] OR LUNABELL [tiab] OR "IKH-01" [tiab] OR Drospirenone [tiab] OR YAZ [tiab] OR "SH-T00186" [tiab] OR "BAY-86-5300" [tiab] OR Levonorgestrel [tiab] OR Jemina [tiab] OR "NPC-16" [tiab] OR Dienogest [tiab] OR "MJR-35" [tiab]	213,788
#5	(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh])	1,377,063
#6	non-Randomized Controlled Trials as Topic[mh] OR Controlled clinical trial [pt] OR Controlled Clinical Trials as Topic [mh] OR comparative study [pt] OR Clinical trial [pt] OR clinical trial [mh] OR Clinical trials as topic [mh] OR cross-over studies [mh]	2,868,639
#7	meta-analysis [pt] OR meta-analysis [mh] OR "meta-analysis" [All] OR (systematic [sb] AND review [pt]) OR "systematic review" [All]	348,803
#8	#5 OR #6 OR #7	3,481,664
#9	#3 AND #4 AND #8	231
#10	(#9) AND (1962:2021/08/31 [pdat])	231

Table S2: Search Strategy in ICHUSHI

#1	"dysmenorrhea"	4199
#2	"Gestagen" OR "Progestin" OR "progesterone" OR "Progestin" OR "Progestogen" OR "Estrogen" OR "Oestrogen" OR "Dydrogesterone" OR "Duphaston" OR "Chlormadinone-Acetate" OR "Lutoral" OR "Norgestrel" OR "Ethinylestradiol" OR "PLANOVAR" OR "LUNABELL" OR "IKH-01" OR "Drospirenone" OR "YAZ" OR "SH-T00186" OR "BAY-86-5300" OR "Levonorgestrel" OR "Jemina" OR "NPC-16" OR "Dienogest" OR "MJR-35"	68,920
#3	"Clinical trials" OR "Clinical trial" OR "Clinical study" OR "Clinical studies" OR "Clinical research" OR "Comparative study" OR "Comparative studies" OR "Comparative research" OR "comparison study" OR "comparison research" OR "Meta-analysis" OR "Systematic Review"	516,305
#4	#1 and #2 and #3	83
#5	#4 and (PDAT=//:2021/8/31)	83

Note: Japanese words originally included in the search strategy were translated in English and overlapped words with original English search words were left out from the table.

Table S3: Extracted information

Article ID	Intervention/ Comparator	Age	Number of cases		Dysmenorrhea Score		Visual Analogue Scale		Assessment time point (week)	Assessment duration in the original study (week)
			Primary	Secondary	Primary	Secondary	Primary	Secondary		
Harada et al. 2008	NET/EE LD-cyclic	31.7 (5.6)	NA	49	NA	−2.0 (1.50)	NA	−31.1 (28.48)	16	16
	Placebo	31.5 (6.3)	NA	47	NA	−0.6 (1.42)	NA	−9.6 (29.84)	16	16
Harada et al. 2011	NET/EE LD-cyclic	29.1 (6.28)	52	NA	−2.6 (1.42)	NA	−36.0 (21.73)	NA	16	16
	Placebo	29.2 (7.15)	55	NA	−1.4 (1.51)	NA	−20.8 (25.57)	NA	16	16
Harada et al. 2016	NET/EE ULD-cyclic	32.4 (7.29)	55	50	−2.3 (1.66)	−2.3 (1.52)	−32.4 (28.52)	−28.8 (29.36)	16	16
	Placebo	30.4 (7.41)	28	26	−1.9 (1.59)	−0.7 (1.29)	−21.8 (29.80)	−3.6 (28.4)	16	16
	NET/EE LD-cyclic	34.0 (6.93)	NA	47	NA	−1.9 (1.64)	NA	−22.4 (30.6)	16	16
Harada et al. 2022	LNG/EE-cyclic	32.1 (8.25)	41	40	−1.9 (1.15)	−1.7 (1.14)	NA	NA	12 (1–12)	48
	LNG/EE-extended	31.6 (8.80)	44	42	−2.8 (1.13)	−3.3 (1.10)	NA	NA	12 (1–12)	48

Study	Group	Age								
	Placebo	33.1 (7.70)	38	40	−0.8 (1.11)	−0.9 (1.14)	NA	NA	12 (1–12)	48
Momoeda et al. 2010b	DRSP/EE-cyclic	30.9 (5.94)	42	19	−1.79 (1.733)	−2.26 (1.368)	−27.9 (25.49)	−37.3 (22.92)	16	16
	Placebo	30.8 (6.43)	41	17	−1.02 (1.475)	−1.00 (1.696)	−11.3 (25.53)	−7.5 (22.01)	16	16
Momoeda et al. 2017	DRSP/EE-extended	28.9 (6.0)	45	19	−2.6 (1.9)	−2.3 (1.8)	−36.7 (28.4)	−32.8 (23.2)	24	24
	DRSP/EE-cyclic	30.4 (6.6)	66	30	−2.9 (1.8)	−2.0 (1.5)	−40.6 (29.8)	−29.9 (26.4)	24	24
Osuga et al. 2020a	DNG	NA	47	NA	−3.1 (2.1)	NA	−44.31 (27.12)	NA	12	12
	Placebo	NA	46	NA	−1.5 (1.7)	NA	−21.01 (26.77)	NA	12	12
	DRSP/EE-cyclic	NA	47	NA	−2.3 (1.7)	NA	−37.29 (27.03)	NA	12	12
Osuga et al. 2020b	DNG	NA	23	24	−3.3 (1.6)	−3.3 (1.5)	−44.7 (27.3)	−45.2 (29.8)	12	12
	Placebo	NA	23	24	−1.5 (1.6)	−0.6 (1.8)	−15.4 (23.2)	0.9 (27.9)	12	12

Values of Age, Dysmenorrhea score and VAS are presented as mean (SD). The total dysmenorrhea score and VAS were not the primary endpoints of DRSP/EE-extended in Momoeda et al. 2017.

The number of decimal places is not necessarily aligned in Table S3 because the descriptions in each original article were compiled.

DNG dienogest with continuous regimen, *DRSP/EE-cyclic* drospirenone/ethinylestradiol betadex with cyclic regimen, *DRSP/EE-extended* drospirenone/ethinylestradiol betadex with extended regimen, *LNG/EE-cyclic* levonorgestrel/ethinylestradiol with cyclic regimen, *LNG/EE-extended* levonorgestrel/ethinylestradiol with extended regimen, *NET/EE LD-cyclic* norethisterone/ethinylestradiol with cyclic regimen, *NET/EE ULD-cyclic* ultra-low-dose norethisterone/ethinylestradiol with cyclic regimen

NA Not Applicable

Table S4: SUCRA values in network meta-analysis of drug treatments

	Primary dysmenorrhea		Secondary dysmenorrhea	
	Total dysmenorrhea score	VAS	Total dysmenorrhea score	VAS
DNG	0.71	0.96	0.75	0.95
DRSP/EE-cyclic	0.44	0.64	0.42	0.59
DRSP/EE-extended	0.31	0.45	0.51	0.67
LNG/EE-cyclic	0.54	NA	0.28	NA
LNG/EE-extended	0.78	NA	0.71	NA
NET/EE LD-cyclic	0.58	0.55	0.44	0.29
NET/EE ULD-cyclic	0.27	0.37	0.56	0.50
Placebo	0.09	0.02	0.06	0.00

SUCRA surface under the cumulative ranking curves
VAS Visual Analogue Scale
DNG dienogest with continuous regimen, *DRSP/EE-cyclic* drospirenone/ethinylestradiol betadex with cyclic regimen, *DRSP/EE-extended* drospirenone/ethinylestradiol betadex with extended regimen, *LNG/EE-cyclic* levonorgestrel/ethinylestradiol with cyclic regimen, *LNG/EE-extended* levonorgestrel/ethinylestradiol with extended regimen, *NET/EE LD-cyclic* norethisterone/ethinylestradiol with cyclic regimen, *NET/EE ULD-cyclic* ultra-low-dose norethisterone/ethinylestradiol with cyclic regimen

Table S5: SUCRA values in network meta-analysis of administration regimens of drug treatments

	Primary dysmenorrhea		Secondary dysmenorrhea	
	Total dysmenorrhea score	VAS	Total dysmenorrhea score	VAS
Continuous	0.87	0.98	0.86	0.98
Cyclic	0.38	0.59	0.36	0.45
Extended	0.74	0.41	0.77	0.57
Placebo	0.00	0.01	0.00	0.00

The assessment time point of drospirenone/ethinylestradiol betadex with extended regimen were at week 24.
SUCRA surface under the cumulative ranking curves
VAS Visual Analogue Scale
Continuous group, dienogest; extended group, drospirenone/ethinylestradiol betadex with extended regimen and levonorgestrel/ethinylestradiol with extended regimen (note that visual analogue scale was not available for levonorgestrel/ethinylestradiol with extended regimen, so it is included only in the extended group of total dysmenorrhea score); and cyclic group, levonorgestrel/ethinylestradiol with cyclic regimen, norethisterone/ethinylestradiol, ultra-low-dose norethisterone/ethinylestradiol, and drospirenone/ethinylestradiol betadex with cyclic

regimen

	Selection bias Random sequence generation	Selection bias Allocation concealment	Performance bias Blinding (participants and personnel)	Detection bias Blinding (outcome assessment)	Attrition bias Incomplete outcome data	Reporting bias Selective reporting	Other bias Other sources of bias
Harada et al. 2008	+	+	+	+	+	?	+
Harada et al. 2011	+	+	+	+	?	+	+
Harada et al. 2016	+	+	+	+	?	+	+
Harada *et al*. 2021	+	+	+	+	+	+	+
Momoeda et al. 2010a	?	?	−	−	+	?	+
Momoeda et al. 2010b	?	?	?	?	?	?	+
Momoede et al. 2014	?	?	−	−	?	+	?
Momoeda et al. 2017	?	?	−	−	+	+	+
Osuga et al. 2020a	+	+	+	+	?	+	+
Osuga et al. 2020b	+	+	+	+	+	+	+

Figure S1. Risk of bias summary of reviewers' assessments of each risk of bias item in included studies

                                    (a)   (b)

                                    (c)   (d)
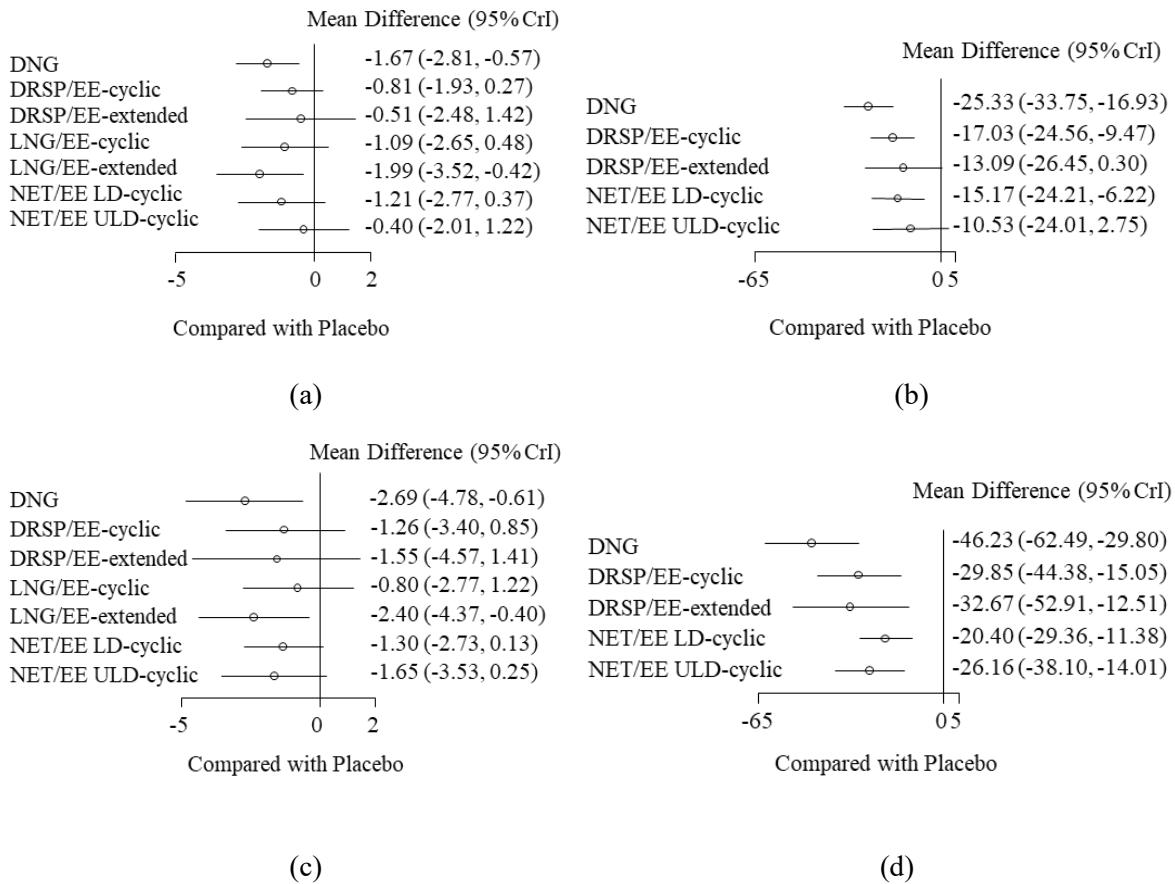
Figure S2. Forest plot of network meta-analysis of drug treatments for dysmenorrhea assessed by total dysmenorrhea score (a, primary dysmenorrhea; c, secondary dysmenorrhea) and visual analogue scale (b, primary dysmenorrhea; d, secondary dysmenorrhea)

The assessment time point of drospirenone/ethinylestradiol betadex with extended regimen were at week 24.

95% CrI 95% credible interval

DNG dienogest with continuous regimen, *DRSP/EE-cyclic* drospirenone/ethinylestradiol betadex with cyclic regimen, *DRSP/EE-extended* drospirenone/ethinylestradiol betadex with extended regimen, *LNG/EE-cyclic* levonorgestrel/ethinylestradiol with cyclic regimen, *LNG/EE-extended* levonorgestrel/ethinylestradiol with extended regimen, *NET/EE LD-cyclic* norethisterone/ethinylestradiol with cyclic regimen, *NET/EE ULD-cyclic* ultra-low-dose norethisterone/ethinylestradiol with cyclic regimen
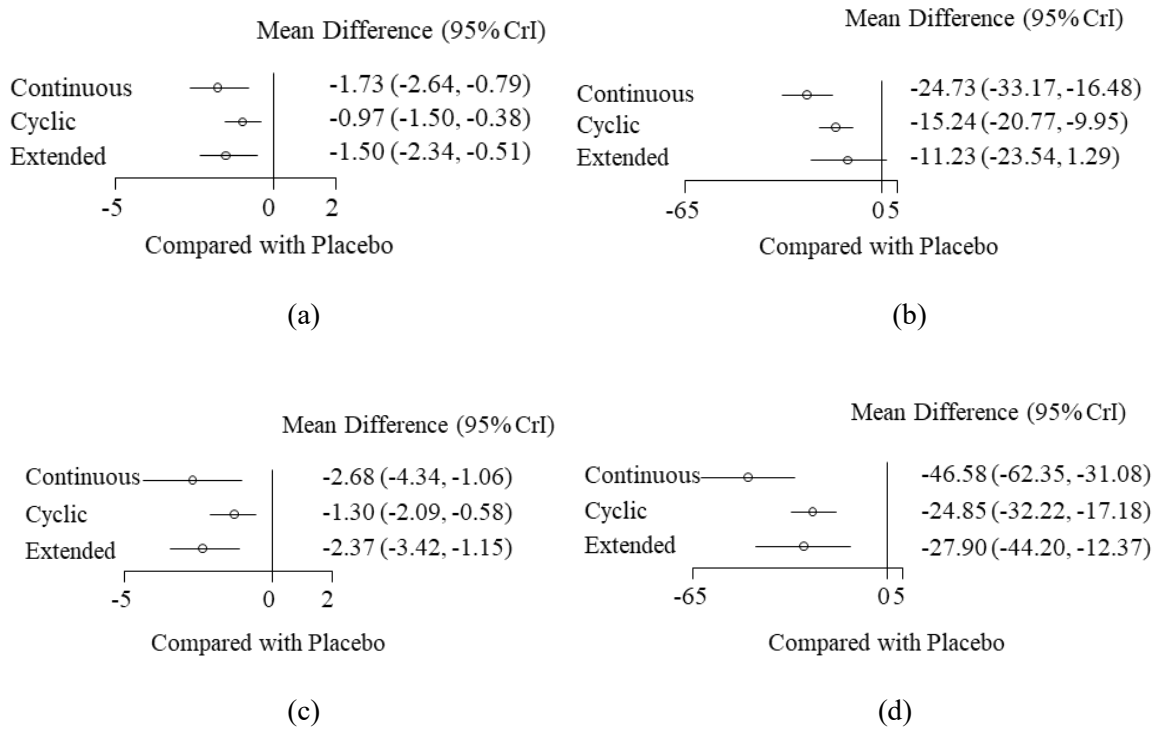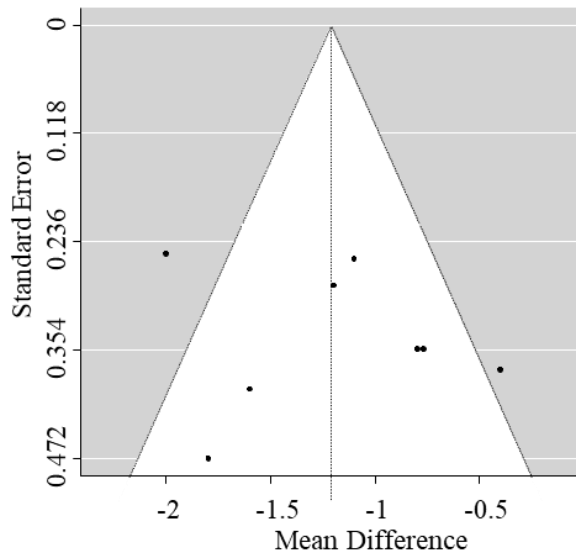
Mean Difference (95% CrI)

Continuous   -1.73 (-2.64, -0.79)
Cyclic   -0.97 (-1.50, -0.38)
Extended   -1.50 (-2.34, -0.51)

-5   0   2

Compared with Placebo

(a)

Mean Difference (95% CrI)

Continuous   -24.73 (-33.17, -16.48)
Cyclic   -15.24 (-20.77, -9.95)
Extended   -11.23 (-23.54, 1.29)

-65   0 5

Compared with Placebo

(b)

Mean Difference (95% CrI)

Continuous   -2.68 (-4.34, -1.06)
Cyclic   -1.30 (-2.09, -0.58)
Extended   -2.37 (-3.42, -1.15)

-5   0   2

Compared with Placebo

(c)

Mean Difference (95% CrI)

Continuous   -46.58 (-62.35, -31.08)
Cyclic   -24.85 (-32.22, -17.18)
Extended   -27.90 (-44.20, -12.37)

-65   0 5

Compared with Placebo

(d)

Figure S3. Forest plot of network meta-analysis of administration regimens of drug treatments for dysmenorrhea assessed by total dysmenorrhea score (a, primary dysmenorrhea; c, secondary dysmenorrhea) and visual analogue scale (b, primary dysmenorrhea; d, secondary dysmenorrhea)
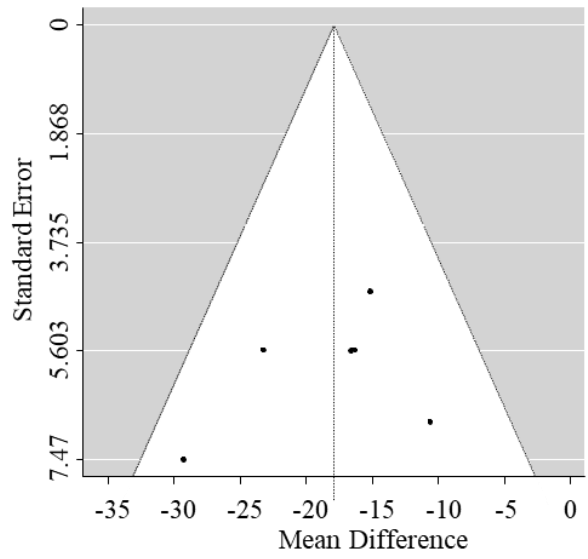
The assessment time point of drospirenone/ethinylestradiol betadex with extended regimen were at week 24.
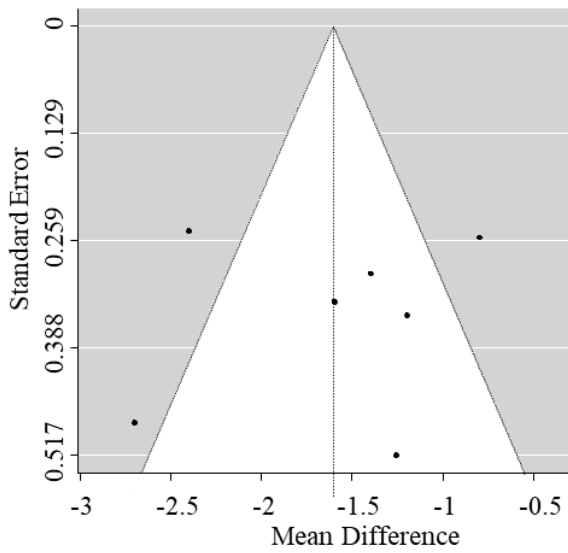
95% CrI 95% credible interval

Continuous group, dienogest continuous; extended group, drospirenone/ethinylestradiol betadex with extended regimen and levonorgestrel/ethinylestradiol with extended regimen (note that visual analogue scale was not available for levonorgestrel/ethinylestradiol with extended regimen, so it is included only in the extended group in Figure S3a, c and not Figure S3b, d); and cyclic group, levonorgestrel/ethinylestradiol with cyclic regimen, norethisterone/ethinylestradiol, ultra-low-dose norethisterone/ethinylestradiol, and drospirenone/ethinylestradiol betadex with cyclic regimen
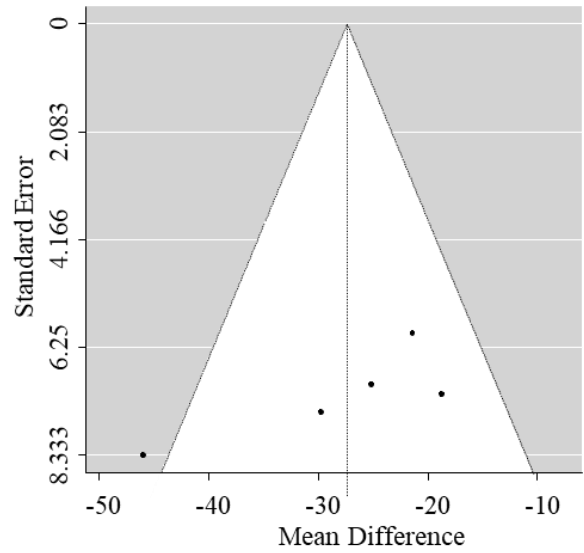
Figure S4. Funnel plot on dysmenorrhea assessed by total dysmenorrhea score (a, primary dysmenorrhea; c, secondary dysmenorrhea) and visual analogue scale (b, primary dysmenorrhea; d, secondary dysmenorrhea)