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APPENDIX

Search Strategy

PubMed, EMBASE, Web of Science, Scopus, Physiotherapy Evidence Database, and Cochrane Database of Systematic Reviews were searched for results through June 14, 2016. These databases were queried using: (menstrual cycle) AND (knee); (ACL) AND (menstrual cycle); (ACL injury) AND (menstrual cycle). Search terms were intentionally broad to maximize and improve generalizability of results. The search was not limited by language or study type.

Statistical Methods

The average effect sizes for both outcomes were calculated using the random effects meta-analysis models implemented in R package metafor[45]. All models were estimated by the restricted maximum likelihood (REML). For laxity, a difference of zero corresponded to no difference between phases. For ACL tear rate, the null effect (i.e., the effect size expected under equal risks in ACL tear for the 2 phases) was proportional to the duration of the compared phases. As the average effect in the meta-analysis model was calculated on the logit scale, it was first back-transformed from the logit (p) scale to the probability (*P*) scale. The transformed average effect (p) was then compared to the probability expected by the durations of the 2 compared phases. Null effect for the different phases was as follows: 5/14 for the 5-day ovulatory phase compared to the 9-day follicular phase, 14/23 for the 14-day luteal phase compared to the 9-day follicular phase, 14/19 for the 14-day luteal phase compared to the 5-day ovulatory phase, and 14/28 for the 14-day luteal phase compared to the 14-day follicular and ovulatory phases combined.

Confidence intervals for the per-study and for the average effects were calculated using the Wald-type theory (point estimate ± 1.96 SE.) The meta-analysis results are displayed using forest plots. Normal quantile-quantile plots were used to assess the departures of the between-study distribution of the effect size and to look for outliers. The DFBETA statistic was used to locate influential studies. Heterogeneity statistics (I^2 and tau) representing the proportion of the total variance attributable to the between-study variance and standard deviations were calculated for all meta-analyses. Meta-regressions were used to predict the between-study differences in the effect size according to the publication year, phase method (“hormone” versus “menstrual event” versus “other”), laxity method (KT2000™ versus KT1000™), athlete population (yes/no), and mean age. For each meta-analysis, the regression test for funnel plot asymmetry was carried out to test for publication bias. Analysis was carried out in R, version 3.3.1. The meta-analysis was implemented in R package metafor[45]. A *P*-value < 0.05 was used to denote statistical significance.

Heterogeneity and publication bias statistics for the ACL tear meta-analyses are shown in Table A1. The effect of study characteristics on ACL tear period outcomes with meta-regression are shown in Table A2. Heterogeneity and publication bias statistics for the laxity meta-analyses are shown in Table A3. The effect of study characteristics on the laxity differences with meta-regression are shown in Table A4.

A comparison of studies using phase classification with hormones, menstrual events or other methods is shown in Figure A1.

The sensitivity analysis for the meta-analysis of laxity difference is shown in Figure A2.

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Table A1. Heterogeneity and publication bias statistics for the anterior cruciate ligament tear meta-analyses.

Outcome (logit of ratio)	I^2	τ	Asymmetry p
O/(F+O)	84%	1.4	0.3
L/(F+L)	60%	0.6	0.2
L/(O+L)	77%	1.0	0.13
L/(F+O+L)	50%	0.4	0.7

F = # Follicular cases, O = # Ovulatory cases, L = # Luteal cases

I^2 = proportion of the overall variance in the logit(p) that was due to between-study variance

τ = the between-study variance on the logit(p) scale

Asymmetry p = *P*-value from the Regression Test for Funnel Plot Asymmetry (publication bias)

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Table A2. Effect of study characteristics on the anterior cruciate ligament tear phase outcomes. Meta-regressions.

	Outcome = O/(F+O)		Outcome = L/(F+L)		Outcome = L/(O+L)		Outcome = L/(F+O+L)	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Publication year, per 10 years	1.88 (0.03-108.51)	0.8	0.20 (0.03-1.52)	0.12	0.14 (0.01-1.77)	0.13	0.47 (0.16-1.37)	0.2
Phase method		0.6		0.3		0.9		0.04
Hormones	1.00 (ref.)	-	1.00 (ref.)	-	1.00 (ref.)	-	1.00 (ref.)	-
Menstrual event	0.69 (0.01-59.14)	0.9	1.10 (0.13-9.50)	0.9	1.62 (0.03-87.24)	0.8	1.57 (0.36-6.91)	0.5
Other means	3.72 (0.20-69.41)	0.4	2.56 (0.70-9.41)	0.2	0.74 (0.06-9.04)	0.8	1.90 (1.16-3.11)	0.01
Athlete population, Y vs. N	-	-	-	-	-	-	1.10 (0.45-2.68)	0.8
Mean age, per 10 years	0.47 (0.13-1.72)	0.3	0.53 (0.08-3.48)	0.5	2.07 (0.06-70.60)	0.7	1.00 (0.91-1.09)	0.9

F = # Follicular cases, O = # Ovulatory cases, L = # Luteal cases.

Table A3. Heterogeneity and publication bias statistics for the laxity meta-analyses.

Outcome (difference in mean laxity)	I^2	τ	Asymmetry p
Ovulatory minus Follicular	51%	0.42	0.04
Ovulatory minus Follicular, Khowailed w. SE	0%	0.00	0.5
Ovulatory minus Follicular, Khowailed excluded	0%	0.00	0.8
Luteal minus Follicular	0%	0.00	0.9
Luteal minus Ovulatory	0%	0.00	1.0

I^2 = proportion of the overall variance was due to between-study variance

τ = the between-study variance

Asymmetry p = *P* value from the Regression Test for Funnel Plot Asymmetry (publication bias)

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Table A4. Effect of study characteristics on the laxity differences. Meta-regressions.

	Outcome = O-F		Outcome = O-F, Khowailed w. SE		Outcome = O-F, Khowailed excluded		Outcome = L-F		Outcome = L-O	
	coef (95% CI)	*p*	*coef (95% CI)*	*p*	*coef (95% CI)*	*p*	*coef (95% CI)*	*p*	*coef (95% CI)*	*p*
Publication year, per 10 years	0.82 (0.31, 1.33)	0.002	0.36 (-0.23, 0.95)	0.2	-0.04 (-0.74, 0.67)	0.9	-0.07 (-0.67, 0.52)	0.8	-0.37 (-1.08, 0.33)	0.3
Phase method		0.4		0.5		0.7		0.9		0.8
Hormones	0.00 (ref.)	-	0.00 (ref.)	-	0.00 (ref.)	-	0.00 (ref.)	-	0.00 (ref.)	-
Menstrual event	-0.47 (-1.19, 0.24)	0.2	-0.32 (-0.86, 0.22)	0.2	-0.23 (-0.78, 0.31)	0.4	0.10 (-0.38, 0.58)	0.7	0.19 (-0.35, 0.73)	0.5
Other means	-0.26 (-1.04, 0.52)	0.5	-0.12 (-0.70, 0.46)	0.7	-0.03 (-0.61, 0.55)	0.9	-0.00 (-0.58, 0.58)	1	0.09 (-0.50, 0.68)	0.8
KT2000 vs. KT1000	0.22 (-0.52, 0.96)	0.6	0.15 (-0.38, 0.68)	0.6	0.08 (-0.45, 0.61)	0.8	0.25 (-0.29, 0.79)	0.4	0.07 (-0.47, 0.60)	0.8
Athlete population, Y vs. N	-0.29 (-0.92, 0.34)	0.4	-0.08 (-0.57, 0.42)	0.8	0.13 (-0.39, 0.65)	0.6	0.05 (-0.44, 0.55)	0.8	-0.20 (-0.72, 0.32)	0.4
Mean age, per 10 years	0.56 (-0.42, 1.53)	0.3	0.18 (-0.59, 0.95)	0.6	-0.08 (-0.88, 0.72)	0.8	0.20 (-0.56, 0.96)	0.6	0.35 (-0.40, 1.11)	0.4

F = mean Follicular laxity, O = mean Ovulatory laxity, L = mean Luteal laxity

Figure A1. Comparison of studies using phase classification with hormones, menstrual events or other methods.

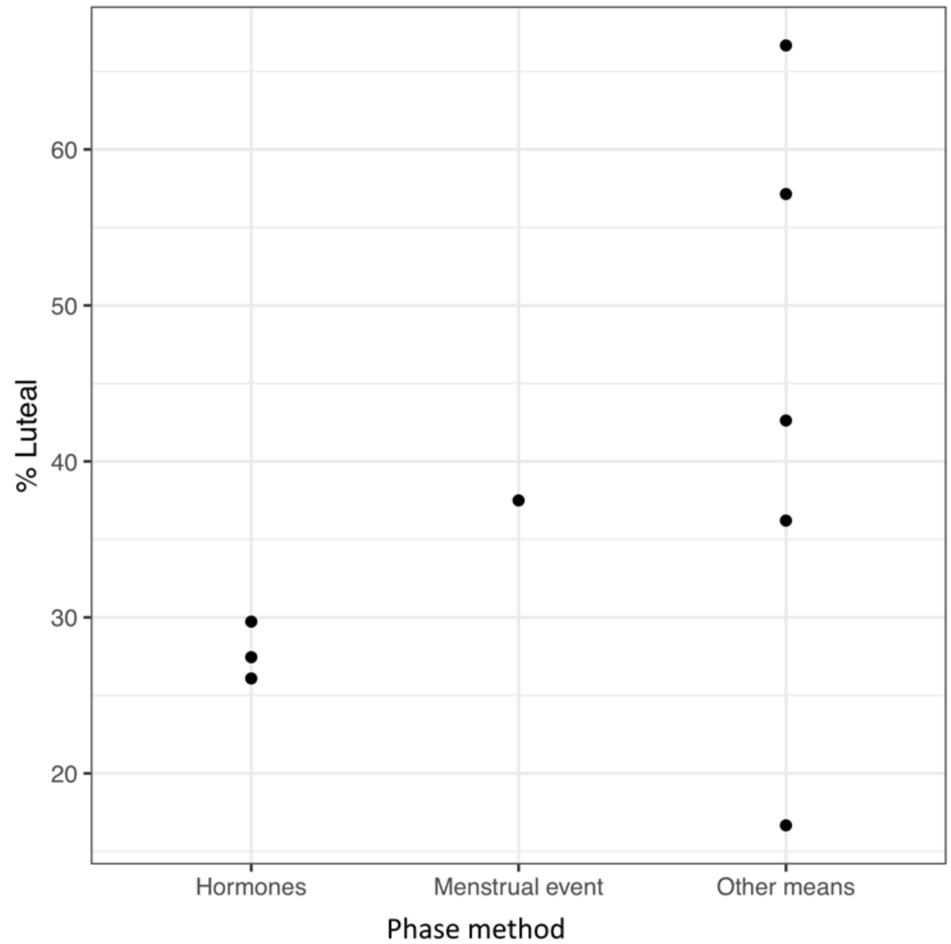

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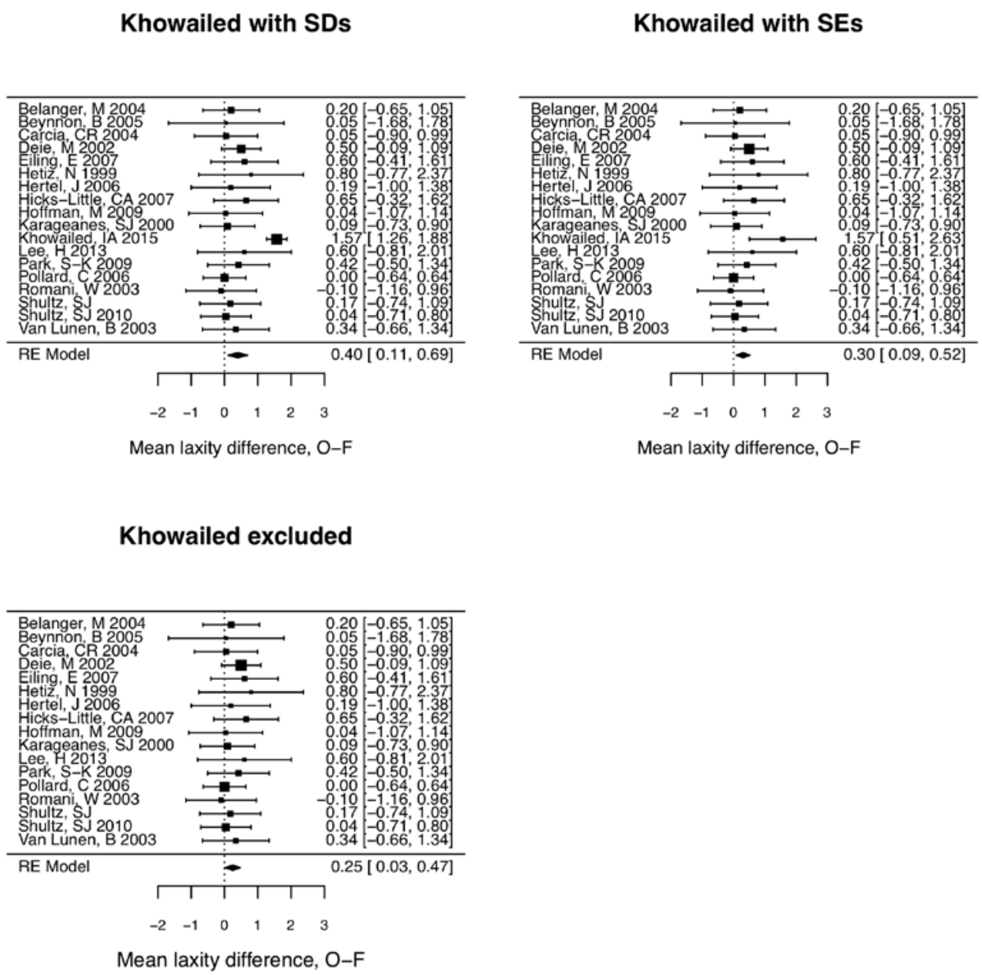
Figure A2. Sensitivity analysis for the meta-analysis of laxity difference.



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