Web Appendix

Hayden et al. Exercise treatment effect modifiers in persistent low back pain:
An individual participant data meta-analysis of 27 randomized controlled trials

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Appendix 1 – Statistical Models and Code.

Statistical model for one-stage IPD treatment effect modifier analysis and sample statistical code (adjusted models)

1A. Mathematical model for one-stage IPD analysis.

$$Y_{ij} = \gamma_{0j} + \gamma_1\left(Base_{ij}\right) + \gamma_2\left(Intervention_{ij}\right) + \gamma_3\left(Age_{ij}\right) + \gamma_4\left(Sex_{ij}\right) + \gamma_5\left(X_{ij}\right) + \gamma_6\left(X_{ij}:Intervention_{ij}\right)$$

$$+ \mu_1\left(Base_{ij}\right) + \mu_2\left(Intervention_{ij}\right) + \mu_3\left(Age_{ij}\right) + \mu_4\left(Sex_{ij}\right) + \mu_5\left(X_{ij}\right) + \mu_6\left(X_{ij}:Intervention_{ij}\right)$$

$$+ \epsilon_{ij}$$

$$\mu_i \sim N(0, {\tau_i}^2)$$

γ_{0j}	Study-specific intercept value
γ_i	Fixed effect for variable i
X	Variable X, one of the 19 subject variables studied in the tables
μ_i	Random effect for variable i
τ_i	Estimated variance for random effect i

1B. Sample statistical code for overall treatment effect models in Stata.

```
mixed painT1 pain_b_cent i.intervention i.study || study:intervention
pain_b_cent, nocons

mixed disT1 dis_b_cent i.intervention i.study || study:intervention dis_b_cent,
nocons

melogit globalimprove dis_b_cent i.intervention i.study || study:intervention
dis_b_cent, nocons or
```

1C. Sample statistical code for treatment effect modification models in R.

```
#Building the RE models for the IPD-MA on back pain exercise
library(readstata13)
library(lme4)
library(ggplot2)
library(cowplot)
library(emmeans)
library(RColorBrewer)
library(xlsx)

dat = read.dta13("FULLIPDDATASET_MASTER_CENTRED.dta")
dat$study = factor(dat$study)
dat$education2 = factor(dat$education2)

dat$globalimprove = dat$globaldisT1
dat$globalimprove[which(dat$globalpainT1==1)] = 1
dat$globalimprove[which(dat$globalpainT1==0 & is.na(dat$globaldisT1))] = 0

#variables for models
vars =
c("age","gender","education2","smoke","PA","BMI","priorLBP","leave","work","deman
ds","genhealth_con","mental_con","avoid","support","durepi","dis_b","pain_b","any
legpain","Rx_b","comply")
```

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```
##getting the centred variables
vars.cent = gsub("\\_con","",gsub("BMI","bmi",paste0(vars,"_cent")))

###################################
# MODEL BUILDING LOOPS
# We chose to build each loop individually for ease of navigation
# each loop creates a list of models for each of the variables
# the naming convention of the lists is
# outcome[.cent].(unadjusted|adjusted)[.re][.forest]
# outcome = painT1, disT1 or gi
# cent indicates if the variables were centred
# unadjusted|adjusted indicates if the models are adjusted for age and gender
# re indicates if the predictors are considered as fixed effects only, or
fixed+random.  Intervention ALWAYS has a re
# forest indicates that the models are for the forest plots (i.e. that all the
predictors are categorical)
###################################

####################################
#RE-Models with centered variables
####################################
#Pain-Unadjusted-Random-Centred
sink("RLOG-painT1_centred_unadjusted_re.log")
painT1.cent.unadjusted.re = list()
for(i in vars.cent){
    form.painT1.cent.unadjusted.re =
sprintf("pain_T1~study+pain_b_cent+intervention*%s+(-
1+pain_b_cent+%s*intervention||study)",i,i)
    painT1.cent.unadjusted.re[[i]] =
lmer(form.painT1.cent.unadjusted.re,data=dat,REML=FALSE)
    print(summary(painT1.cent.unadjusted.re[[i]]))
}
sink()

#Pain-Adjusted-Random-Centred
sink("RLOG-painT1_centred_adjusted_re.log")
painT1.cent.adjusted.re = list()
for(i in vars.cent){
    form.painT1.cent.adjusted.re =
sprintf("pain_T1~study+pain_b_cent+intervention*%s+age_cent+gender_cent+(-
1+pain_b_cent+age_cent+gender_cent+%s*intervention||study)",i,i)
    painT1.cent.adjusted.re[[i]] =
lmer(form.painT1.cent.adjusted.re,data=dat,REML=FALSE)
    print(summary(painT1.cent.adjusted.re[[i]]))
}
sink()

#Dis-Unadjusted-Random-Centred
sink("RLOG-disT1_centred_unadjusted_re.log")
disT1.cent.unadjusted.re = list()
for(i in vars.cent){
    form.disT1.cent.unadjusted.re =
sprintf("dis_T1~study+dis_b_cent+intervention*%s+(-
1+dis_b_cent+%s*intervention||study)",i,i)
    disT1.cent.unadjusted.re[[i]] =
lmer(form.disT1.cent.unadjusted.re,data=dat,REML=FALSE)
```

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```
        print(summary(disT1.cent.unadjusted.re[[i]]))
}
sink()

#Dis-Adjusted-Random-Centred
sink("RLOG-disT1_centred_adjusted_re.log")
disT1.cent.adjusted.re = list()
for(i in vars.cent){
    form.disT1.cent.adjusted.re =
sprintf("dis_T1~study+dis_b_cent+intervention*%s+age_cent+gender_cent+(-
1+dis_b_cent+age_cent+gender_cent+%s*intervention||study)",i,i)
    disT1.cent.adjusted.re[[i]] =
lmer(form.disT1.cent.adjusted.re,data=dat,REML=FALSE)
    print(summary(disT1.cent.adjusted.re[[i]]))
}
sink()

#GI-Unadjusted-Random-Centred
sink("RLOG-gi_centred_unadjusted_re.log")
gi.cent.unadjusted.re = list()
for(i in vars.cent){
    form.gi.cent.unadjusted.re =
sprintf("globalimprove~study+dis_b_cent+intervention*%s+(-
1+dis_b_cent+%s*intervention||study)",i,i)
    gi.cent.unadjusted.re[[i]] =
glmer(form.gi.cent.unadjusted.re,data=dat,family=binomial)
    print(summary(gi.cent.unadjusted.re[[i]]))
}
sink()

#GI-Adjusted-Random-Centred
sink("RLOG-gi_centred_adjusted_re.log")
gi.cent.adjusted.re = list()
for(i in vars.cent){
    form.gi.cent.adjusted.re =
sprintf("globalimprove~study+dis_b_cent+gender_cent+age_cent+intervention*%s+(-
1+dis_b_cent+gender_cent+age_cent+%s*intervention||study)",i,i)
    gi.cent.adjusted.re[[i]] =
glmer(form.gi.cent.adjusted.re,data=dat,family=binomial)
    print(summary(gi.cent.adjusted.re[[i]]))
}
sink()

####################
# Forest Plot Models
# forest plot models including the centred variables
####################
vars.forest =
c("age_cat","gender","education2","smoke","PA","bmi_cat","priorLBP","leave","work
","demands","genhealth_med","mentalhealth_med","avoid_med","support","chronic_cat
","dis_cat","pain_cat","anylegpain","Rx_b","comply")
sink("RLOG-forestPlots.log")
painT1.adjusted.re.forest = disT1.adjusted.re.forest = gi.adjusted.re.forest =
list()
#because age_cat and gender are different from the controlling variables they
need to be fit differently
i='age_cat'
```
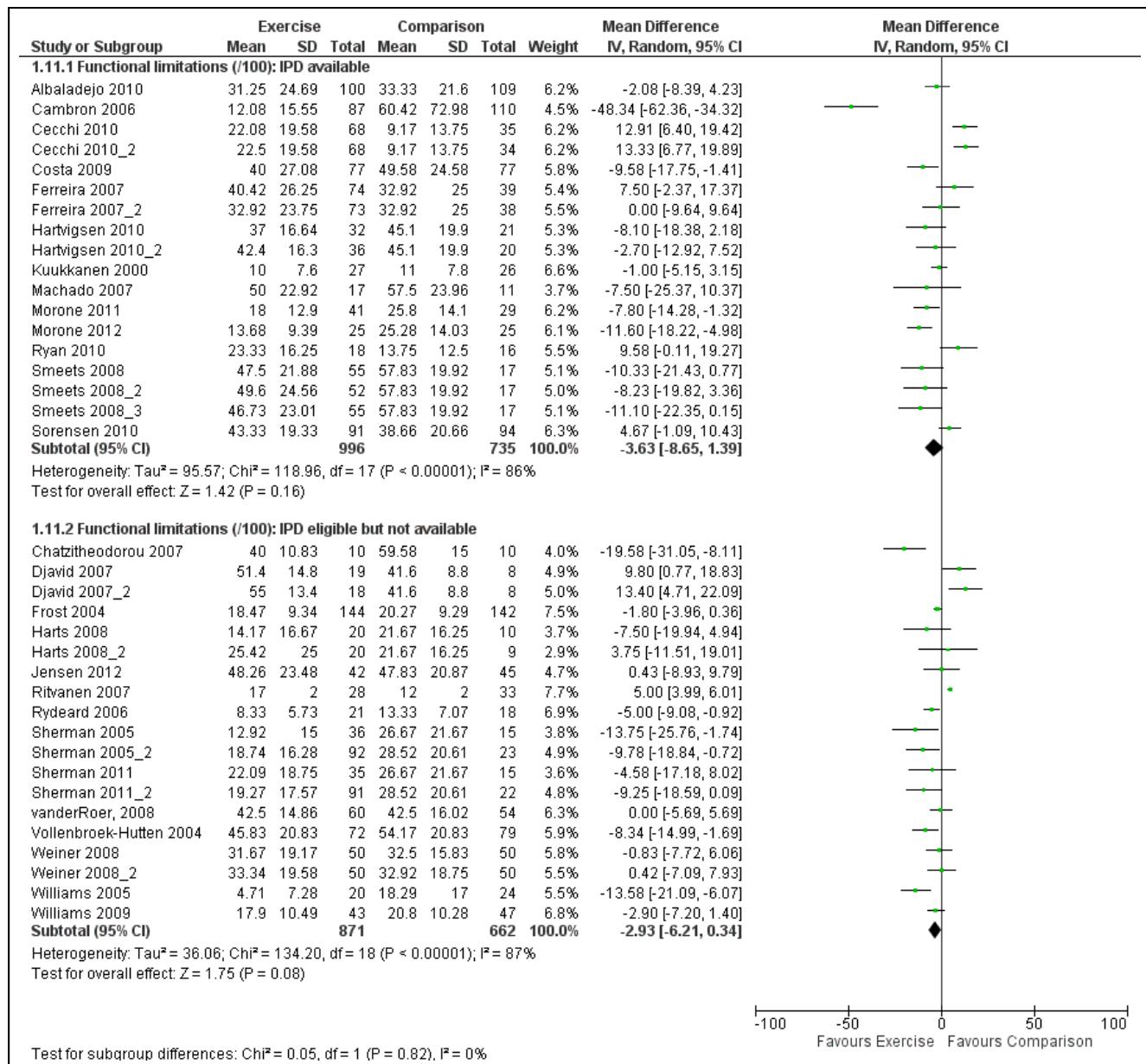
4

```
painT1.adjusted.re.forest[[i]] =
lmer(pain_T1~study+pain_b_cent+gender_cent+intervention*age_cat+(-
1+pain_b_cent+gender_cent+age_cat*intervention||study),data=dat,REML=FALSE)
disT1.adjusted.re.forest[[i]] =
lmer(dis_T1~study+dis_b_cent+gender_cent+intervention*age_cat+(-
1+dis_b_cent+gender_cent+age_cat*intervention||study),data=dat,REML=FALSE)
gi.adjusted.re.forest[[i]] =
glmer(globalimprove~study+dis_b_cent+gender_cent+intervention*age_cat+(-
1+dis_b_cent+gender_cent+age_cat*intervention||study),family=binomial,data=dat)
print(summary(painT1.adjusted.re.forest[[i]]))
print(summary(disT1.adjusted.re.forest[[i]]))
print(summary(gi.adjusted.re.forest[[i]]))
i='gender'
dat[,i] = factor(dat[,i])
painT1.adjusted.re.forest[[i]] =
lmer(pain_T1~study+pain_b_cent+age_cent+intervention*gender+(-
1+pain_b_cent+age_cent+gender*intervention||study),data=dat,REML=FALSE)
disT1.adjusted.re.forest[[i]] =
lmer(dis_T1~study+dis_b_cent+age_cent+intervention*gender+(-
1+dis_b_cent+age_cent+gender*intervention||study),data=dat,REML=FALSE)
gi.adjusted.re.forest[[i]] =
glmer(globalimprove~study+dis_b_cent+age_cent+intervention*gender+(-
1+dis_b_cent+age_cent+gender*intervention||study),family=binomial,data=dat)
print(summary(painT1.adjusted.re.forest[[i]]))
print(summary(disT1.adjusted.re.forest[[i]]))
print(summary(gi.adjusted.re.forest[[i]]))
for(i in vars.forest[-(1:2)]){
    form01 =
sprintf("pain_T1~study+pain_b_cent+gender_cent+age_cent+intervention*%s+(-
1+pain_b_cent+gender_cent+age_cent+%s*intervention||study)",i,i)
    form02 =
sprintf("dis_T1~study+dis_b_cent+gender_cent+age_cent+intervention*%s+(-
1+dis_b_cent+gender_cent+age_cent+%s*intervention||study)",i,i)
    form03 =
sprintf("globalimprove~study+dis_b_cent+gender_cent+age_cent+intervention*%s+(-
1+dis_b_cent+gender_cent+age_cent+%s*intervention||study)",i,i)
    if(class(dat[,i])!='factor')
        dat[,i] = factor(dat[,i])
    #painT1.adjusted.re.forest[[i]] = lmer(form01,data=dat,REML=FALSE)
    #disT1.adjusted.re.forest[[i]] = lmer(form02,data=dat,REML=FALSE)
    gi.adjusted.re.forest[[i]] = glmer(form03,family=binomial,data=dat)
    print(summary(painT1.adjusted.re.forest[[i]]))
    print(summary(disT1.adjusted.re.forest[[i]]))
    print(summary(gi.adjusted.re.forest[[i]]))
}
sink()

#need to get the CIs from the forest data
painT1.adjusted.re.forest.ci = disT1.adjusted.re.forest.ci =
gi.adjusted.re.forest.ci = NA
getCI = function(est,exp=TRUE){
    s=summary(est$contrasts)
    LCL=s$estimate-qnorm(0.975)*s$SE
    UCL=s$estimate+qnorm(0.975)*s$SE
    #these are all presented in the wrong order compared to the orig results
    #so I need to flip them
    out = cbind(EST=-s$estimate,LCL=-UCL,UCL=-LCL)
```

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```
    rownames(out)=s[[i]]
    if(exp)
        return(exp(out))
    else
        return(out)
}

for(i in vars.forest){
    if(class(dat[,i])!='factor')
        dat[,i] = factor(dat[,i])
    #painT1
    est =
emmeans(painT1.adjusted.re.forest[[i]],as.formula(paste0("pairwise~intervention|"
,i)),at=list(intervention=c(1,0)),emm_options(pbkrtest.limit = 0))
    ci=getCI(est,FALSE)
    temp = data.frame(cbind(vars=NA,rbind(NA,ci),studyCount=NA,N=NA))
    temp$vars = c(i,rownames(ci))
    temp$studyCount[1] = ngrps(painT1.adjusted.re.forest[[i]])
    temp$N[1] = nobs(painT1.adjusted.re.forest[[i]])
    painT1.adjusted.re.forest.ci = rbind(painT1.adjusted.re.forest.ci,temp)
    #disT1
    est =
emmeans(disT1.adjusted.re.forest[[i]],as.formula(paste0("pairwise~intervention|",
i)),at=list(intervention=c(1,0)),emm_options(pbkrtest.limit = 0))
    ci=getCI(est,FALSE)
    temp = data.frame(cbind(vars=NA,rbind(NA,ci),studyCount=NA,N=NA))
    temp$vars = c(i,rownames(ci))
    temp$studyCount[1] = ngrps(disT1.adjusted.re.forest[[i]])
    temp$N[1] = nobs(disT1.adjusted.re.forest[[i]])
    disT1.adjusted.re.forest.ci = rbind(disT1.adjusted.re.forest.ci,temp)
    #gi
    est =
emmeans(gi.adjusted.re.forest[[i]],as.formula(paste0("pairwise~intervention|",i))
,at=list(intervention=c(1,0)),emm_options(pbkrtest.limit = 0))
    ci=getCI(est,TRUE)
    temp = data.frame(cbind(vars=NA,rbind(NA,ci),studyCount=NA,N=NA))
    temp$vars = c(i,rownames(ci))
    temp$studyCount[1] = ngrps(gi.adjusted.re.forest[[i]])
    temp$N[1] = nobs(gi.adjusted.re.forest[[i]])
    gi.adjusted.re.forest.ci = rbind(gi.adjusted.re.forest.ci,temp)
}
```

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Appendix 2 (Figure) - Aggregate Meta-Analysis Results, Functional Limitations. Aggregate meta-analysis results, from published estimates, for studies with IPD available and eligible studies that did not provide data for comparison of exercise therapy with other treatment comparisons on functional limitations outcome (/100) at earliest follow-up period.[*]

Study or Subgroup	Exercise Mean	SD	Total	Comparison Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.11.1 Functional limitations (/100): IPD available								
Albaladejo 2010	31.25	24.69	100	33.33	21.6	109	6.2%	-2.08 [-8.39, 4.23]
Cambron 2006	12.08	15.55	87	60.42	72.98	110	4.5%	-48.34 [-62.36, -34.32]
Cecchi 2010	22.08	19.58	68	9.17	13.75	35	6.2%	12.91 [6.40, 19.42]
Cecchi 2010_2	22.5	19.58	68	9.17	13.75	34	6.2%	13.33 [6.77, 19.89]
Costa 2009	40	27.08	77	49.58	24.58	77	5.8%	-9.58 [-17.75, -1.41]
Ferreira 2007	40.42	26.25	74	32.92	25	39	5.4%	7.50 [-2.37, 17.37]
Ferreira 2007_2	32.92	23.75	73	32.92	25	38	5.5%	0.00 [-9.64, 9.64]
Hartvigsen 2010	37	16.64	32	45.1	19.9	21	5.3%	-8.10 [-18.38, 2.18]
Hartvigsen 2010_2	42.4	16.3	36	45.1	19.9	20	5.3%	-2.70 [-12.92, 7.52]
Kuukkanen 2000	10	7.6	27	11	7.8	26	6.6%	-1.00 [-5.15, 3.15]
Machado 2007	50	22.92	17	57.5	23.96	11	3.7%	-7.50 [-25.37, 10.37]
Morone 2011	18	12.9	41	25.8	14.1	29	6.2%	-7.80 [-14.28, -1.32]
Morone 2012	13.68	9.39	25	25.28	14.03	25	6.1%	-11.60 [-18.22, -4.98]
Ryan 2010	23.33	16.25	18	13.75	12.5	16	5.5%	9.58 [-0.11, 19.27]
Smeets 2008	47.5	21.88	55	57.83	19.92	17	5.1%	-10.33 [-21.43, 0.77]
Smeets 2008_2	49.6	24.56	52	57.83	19.92	17	5.0%	-8.23 [-19.82, 3.36]
Smeets 2008_3	46.73	23.01	55	57.83	19.92	17	5.1%	-11.10 [-22.35, 0.15]
Sorensen 2010	43.33	19.33	91	38.66	20.66	94	6.3%	4.67 [-1.09, 10.43]
Subtotal (95% CI)			**996**			**735**	**100.0%**	**-3.63 [-8.65, 1.39]**
Heterogeneity: Tau² = 95.57; Chi² = 118.96, df = 17 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 1.42 (P = 0.16)								
1.11.2 Functional limitations (/100): IPD eligible but not available								
Chatzitheodorou 2007	40	10.83	10	59.58	15	10	4.0%	-19.58 [-31.05, -8.11]
Djavid 2007	51.4	14.8	19	41.6	8.8	8	4.9%	9.80 [0.77, 18.83]
Djavid 2007_2	55	13.4	18	41.6	8.8	8	5.0%	13.40 [4.71, 22.09]
Frost 2004	18.47	9.34	144	20.27	9.29	142	7.5%	-1.80 [-3.96, 0.36]
Harts 2008	14.17	16.67	20	21.67	16.25	10	3.7%	-7.50 [-19.94, 4.94]
Harts 2008_2	25.42	25	20	21.67	16.25	9	2.9%	3.75 [-11.51, 19.01]
Jensen 2012	48.26	23.48	42	47.83	20.87	45	4.7%	0.43 [-8.93, 9.79]
Ritvanen 2007	17	2	28	12	2	33	7.7%	5.00 [3.99, 6.01]
Rydeard 2006	8.33	5.73	21	13.33	7.07	18	6.9%	-5.00 [-9.08, -0.92]
Sherman 2005	12.92	15	36	26.67	21.67	15	3.8%	-13.75 [-25.76, -1.74]
Sherman 2005_2	18.74	16.28	92	28.52	20.61	23	4.9%	-9.78 [-18.84, -0.72]
Sherman 2011	22.09	18.75	35	26.67	21.67	15	3.6%	-4.58 [-17.18, 8.02]
Sherman 2011_2	19.27	17.57	91	28.52	20.61	22	4.8%	-9.25 [-18.59, 0.09]
vanderRoer, 2008	42.5	14.86	60	42.5	16.02	54	6.3%	0.00 [-5.69, 5.69]
Vollenbroek-Hutten 2004	45.83	20.83	72	54.17	20.83	79	5.9%	-8.34 [-14.99, -1.69]
Weiner 2008	31.67	19.17	50	32.5	15.83	50	5.8%	-0.83 [-7.72, 6.06]
Weiner 2008_2	33.34	19.58	50	32.92	18.75	50	5.5%	0.42 [-7.09, 7.93]
Williams 2005	4.71	7.28	20	18.29	17	24	5.5%	-13.58 [-21.09, -6.07]
Williams 2009	17.9	10.49	43	20.8	10.28	47	6.8%	-2.90 [-7.20, 1.40]
Subtotal (95% CI)			**871**			**662**	**100.0%**	**-2.93 [-6.21, 0.34]**
Heterogeneity: Tau² = 36.06; Chi² = 134.20, df = 18 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 1.75 (P = 0.08)								

Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%

[Mean Difference IV, Random, 95% CI forest plot with x-axis from -100 to 100, marked at -100, -50, 0, 50, 100. Labels: Favours Exercise / Favours Comparison]

[*]Synthesizes only trial group data with non-exercise comparison (i.e. all other conservative and no treatment/usual care comparisons), similar to primary analysis in the related Cochrane review (14 studies/19 groups for IPD and 13 studies/18 groups for IPD eligible, but not available); functional limitations outcome (/100). Trials that include only comparisons of different types of exercise are not included.

Appendix 3 (Table) – Pain Outcome, Moderate and Long-Term Follow-Up. Treatment-variable interactions (adjusted results) on continuous pain outcome (0-100) at moderate- (closest to 6 months) and long-term (closest to 12 months) follow-up times. A negative interaction coefficient indicates decreased pain for the variable level (e.g. females) with exercise vs. all other conservative and no treatment/usual care comparisons.

Variable	6 month follow-up				12 month follow-up			
	N studies	n participants	Interaction MD (95% CI)	p-value	N studies	n participants	Interaction MD (95% CI)	p-value
Age (years)	18	2117	0.08 (-0.09, 0.25)	0.36	13	1809	0.13 (-0.09, 0.35)	0.26
Sex								
Male	18	2117	--	--	13	1809	--	--
Female			0.49 (-4.01, 4.99)	0.83			-4.00 (-9.69, 1.70)	0.17
High school education								
High school or less	8	945	--	--	5	585	--	--
Beyond high school			0.06 (-6.40, 6.53)	0.99			-13.36 (-23.60, -3.12)	0.01
Current smoker								
No	8	1156	--	--	7	1080	--	--
Yes			0.06 (-5.56, 5.67)	0.98			2.48 (-4.89, 9.84)	0.51
Regular physical activity								
No	9	1351	--	--	8	1278	--	--
Yes			-0.10 (-5.26, 5.07)				1.06 (-5.60, 7.73)	0.75
BMI	11	1519	0.17 (-0.42, 0.77)	0.57	9	1401	-0.03 (-0.83, 0.76)	0.93
History of LBP								
No	5	554	--	--	4	526	--	--
Yes			-4.74 (-19.46, 9.98)	0.53			18.86 (1.69, 36.02)	0.03
Sick leave (past 12 months)								
No	11	1097	--	--	9	1169	--	--
Yes			-0.48 (-8.69, 7.73)	0.91			-5.09 (-15.21, 5.02)	0.32
Work status								
Unemployed	13	1808	--	--	10	1431	--	--
Employed			0.86 (-7.29, 9.02)	0.84			2.80 (-3.62, 9.23)	0.39
Heavy physical demands								
No	5	794	--	--	6	992	--	--
Yes			2.70 (-7.69, 13.1)	0.61			3.91 (-6.49, 14.32)	0.46
General health (0-100)	9	1026	0.04 (-0.15, 0.23)	0.68	5	738	0.41 (-0.04, 0.86)	0.07
Mental health (0-100)	5	640	0.02 (-0.12, 0.17)	0.75	2	431	N/A*	N/A*
Fear avoidance (0-100)	5	781	0.13 (0.01, 0.26)	0.04	5	597	0.03 (-0.19, 0.25)	0.79
Social support								
No	8	1077	--	--	5	715	--	--
Yes			2.46 (-3.08, 8.00)	0.39			1.11 (-7.84, 10.07)	0.81
Episode duration (months)	9	1069	0.05 (0.02, 0.09)	0.004	7	953	0.03 (-0.03, 0.09)	0.37
Functional limitations (0-100)	17	2042	0.02 (-0.10, 0.14)	0.71	13	1806	-0.04 (-0.19, 0.11)	0.59
Pain intensity (0-100)	18	2117	0.03 (-0.11, 0.16)	0.68	13	1809	-0.09 (-0.25, 0.07)	0.27

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Any leg pain									
No	9	1104	--	--	8	1049	--	--
Yes			3.58 (-4.24, 11.41)	0.37			1.28 (-16.36, 18.91)	0.89
Any LBP medication use									
No	11	1426	--	--	7	1057	--	--
Yes			-3.43 (-9.02, 2.15)	0.23			-4.16 (-11.14, 2.82)	0.24

*An estimate for the interaction could not be obtained due to no participants in the comparison groups; LBP=low back pain.

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Appendix 4 (Table) – Functional Limitations Outcome, Moderate and Long-Term Follow-Up. Treatment-variable interactions (adjusted results) on continuous functional limitations outcome (0-100) at moderate- (closest to 6 months) and long-term (closest to 12 months) follow-up times. A negative interaction coefficient indicates decreased function for the variable level (e.g. females) with exercise vs. all other conservative and no treatment/usual care comparisons.

Variable	6 month follow-up				12 month follow-up			
	N studies	n participants	Interaction MD (95% CI)	p-value	N studies	n participants	Interaction MD (95% CI)	p-value
Age (years)	18	2106	0.13 (-0.01, 0.28)	0.07	14	1796	0.18 (-0.01, 0.38)	0.07
Sex								
Male	18	2106	--	--	14	1796	--	--
Female			-1.55 (-5.77, 2.67)	0.47			-4.68 (-9.60, 0.23)	0.06
High school education								
High school or less	7	870	--	--	6	632	--	--
Beyond high school			-1.07 (-7.07, 4.94)	0.73			-9.87 (-19.81, 0.07)	0.05
Current smoker								
No	8	1153	--	--	7	1055	--	--
Yes			-0.26 (-4.74, 4.22)	0.91			-1.55 (-8.2, 5.11)	0.65
Regular physical activity								
No	10	1407	--	--	10	1351	--	--
Yes			0.76 (-3.19, 4.70)	0.71			-1.50 (-7.10, 4.09)	0.60
BMI	10	1442	0.18 (-0.29, 0.64)	0.46	9	1326	-0.25 (-0.92, 0.43)	0.47
History of LBP								
No	5	554	--	--	5	571	--	--
Yes			-4.30 (-17.32, 8.71)	0.52			-4.11 (-16.28, 8.06)	0.51
Sick leave (past 12 months)								
No	11	1092	--	--	10	1208	--	--
Yes			-0.71 (-8.46, 7.04)	0.86			-1.26 (-9.90, 7.38)	0.77
Work status								
Unemployed	13	1798	--	--	12	1513	--	--
Employed			2.09 (-3.14, 7.32)	0.43			0.31 (-4.91, 5.53)	0.91
Heavy physical demands								
No	5	793	--	--	6	966	--	--
Yes			5.14 (-2.95, 13.22)	0.21			4.59 (-5.28, 14.45)	0.36
General health (0-100)	9	1026	0.004 (-0.15, 0.16)	0.96	6	776	-0.04 (-0.40, 0.32)	0.82
Mental health (0-100)	6	710	0.03 (-0.09, 0.16)	0.61	3	467	N/A[*]	N/A[*]
Fear avoidance (0-100)	6	849	0.10 (-0.02, 0.22)	0.10	5	565	0.003 (-0.18, 0.19)	0.97
Social support								
No	7	1003	--	--	5	715	--	--
Yes			3.83 (-2.39, 10.06)	0.23			1.63 (-7.02, 10.28)	0.71
Episode duration (months)	9	1068	0.05 (-0.003, 0.10)	0.07	8	974	0.03 (-0.02, 0.09)	0.21

Functional limitations (0-100)	18	2106	-0.12 (-0.28, 0.04)	0.14	14	1796	0.04 (-0.13, 0.21)	0.66
Pain intensity (0-100)	17	2036	0.01 (-0.08, 0.11)	0.77	13	1733	-0.08 (-0.20, 0.05)	0.24
Any leg pain								
No	10	1170	--	--	9	1037	--	--
Yes			2.47 (-3.96, 8.90)	0.45			-0.80 (-15.08, 13.49)	0.91
Any LBP medication use								
No	11	1423	--	--	7	1030	--	--
Yes			-3.14 (-9.81, 3.53)	0.36			-6.80 (-12.67, -0.92)	0.02

*An estimate for the interaction could not be obtained due to no participants in the comparison groups; LBP=low back pain.

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Appendix 5 (Table) – Global Recovery Outcome, Moderate and Long-Term Follow-Up. Treatment-variable interactions (adjusted results) on important global recovery outcome (dichotomous) at moderate- (closest to 6 months) and long-term (closest to 12 months) follow-up times. An interaction coefficient above 1 indicates increased likelihood of recovery for the variable level (e.g. females) with exercise vs. all other conservative and no treatment/usual care comparisons.

Variable	6 month follow-up				12 month follow-up			
	N studies	n participants	Interaction OR (95% CI)	p-value	N studies	n participants	Interaction OR (95% CI)	p-value
Age (years)	18	2110	0.99 (0.98, 1.01)	0.45	15	1916	0.99 (0.97, 1.01)	0.28
Sex								
Male	18	2110	--	--	15	1916	--	--
Female			0.92 (0.57, 1.47)	0.72			1.70 (1.03, 2.80)	0.04
High school education								
High school or less	7	872	--	--	6	632	--	--
Beyond high school			0.88 (0.43, 1.81)	0.73			1.93 (0.75, 4.97)	0.17
Current smoker								
No	8	1154	--	--	7	1085	--	--
Yes			1.81 (0.92, 3.56)	0.09			1.89 (0.91, 3.91)	0.09
Regular physical activity								
No	10	1410	--	--	10	1381	--	--
Yes			0.94 (0.54, 1.66)	0.84			0.95 (0.51, 1.77)	0.88
BMI	10	1445	0.97 (0.89, 1.06)	0.47	10	1446	1.02 (0.95, 1.10)	0.52
History of LBP								
No	5	555	--	--	5	572	--	--
Yes			0.98 (0.29, 3.32)	0.97			1.13 (0.31, 4.12)	0.85
Sick leave (past 12 months)								
No	11	1091	--	--	10	1235	--	--
Yes			1.13 (0.44, 2.86)	0.80			1.30 (0.49, 3.45)	0.60
Work status								
Unemployed	13	1800	--	--	12	1539	--	--
Employed			0.85 (0.42, 1.74)	0.66			0.78 (0.43, 1.44)	0.43
Heavy physical demands								
No	5	794	--	--	6	996	--	--
Yes			0.42 (0.13, 1.37)	0.15			0.44 (0.14, 1.37)	0.16
General health (0-100)	9	1025	0.99 (0.97, 1.02)	0.72	6	805	0.99 (0.95, 1.03)	0.66
Mental health (0-100)	6	709	0.99 (0.97, 1.01)	0.40	3	497	N/A[*]	N/A[*]
Fear avoidance (0-100)	6	848	0.99 (0.97, 1.00)	0.14	6	655	1.00 (0.98, 1.02)	0.79
Social support								
No	7	1003	--	--	5	714	--	--
Yes			0.62 (0.32, 1.21)	0.16			1.10 (0.46, 2.61)	0.84
Episode duration (months)	9	1070	1.00 (0.99, 1.00)	0.14	8	1005	1.00 (0.99, 1.00)	0.23

Functional limitations (0-100)	18	2110	1.00 (0.99, 1.02)	0.59	15	1916	1.01 (0.99, 1.02)	0.58
Pain intensity (0-100)	17	2043	1.00 (0.98, 1.01)	0.47	14	1854	1.01 (0.99, 1.02)	0.43
Any leg pain								
No	10	1171	--	--	10	1158	--	--
Yes			0.83 (0.36, 1.93)	0.67			0.79 (0.16, 3.93)	0.77
Any LBP medication use								
No	11	1428	--	--	7	1060	--	--
Yes			1.29 (0.72, 2.30)	0.40			1.32 (0.69, 2.51)	0.40

*An estimate for the interaction could not be obtained due to no participants in the comparison groups; LBP=low back pain.

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Appendix 6 (Table) – Pain Outcome, by Comparison Group Type. Treatment-variable interactions (adjusted results) on continuous pain outcome (0-100), for exercise treatment relative to each of: A. no treatment/usual care and B. other conservative comparisons at follow-up time closest to 3 months. A negative interaction coefficient indicates decreased pain for the variable level (e.g. females) with exercise vs. each comparison type.

Variable	A. No treatment/usual care comparison				B. Other non-exercise conservative comparison			
	N studies	n participants	Interaction MD (95% CI)	p-value	N studies	n participants	Interaction MD (95% CI)	p-value
Age (years)	26	2463	0.18 (-0.06, 0.43)	0.14	26	2846	0.07 (-0.09, 0.23)	0.41
Sex								
Male	26	2463	--	--	26	2846	--	--
Female			-2.10 (-7.98, 3.78)	0.48			-0.95 (-4.82, 2.93)	0.63
High school education								
High school or less	12	1063	--	--	12	1222	--	--
Beyond high school			-8.30 (-16.63, 0.02)	0.05			-1.86 (-7.33, 3.61)	0.51
Current smoker								
No	9	1113	--	--	9	1304	--	--
Yes			1.59 (-8.12, 11.30)	0.75			0.27 (-5.64, 6.18)	0.93
Regular physical activity								
No	11	1356	--	--	11	1552	--	--
Yes			-0.10 (-8.09, 7.90)	0.98			-0.87 (-6.31, 4.57)	0.75
BMI	17	1837	0.78 (0.08, 1.48)	0.03	17	1994	-0.28 (-0.93, 0.37)	0.40
History of LBP								
No	8	827	--	--	8	701	--	--
Yes			-3.92 (-13.76, 5.93)	0.44			N/A[*]	N/A[*]
Sick leave (past 12 months)								
No	14	1457	--	--	14	1459	--	--
Yes			-1.29 (-9.95, 7.37)	0.77			-6.32 (-16.42, 3.79)	0.22
Work status								
Unemployed	18	1876	--	--	18	2266	--	--
Employed			-5.93 (-15.39, 3.54)	0.22			-3.51 (-8.93, 1.91)	0.20
Heavy physical demands								
No	8	1208	--	--	8	1312	--	--
Yes			8.01 (-4.34, 20.37)	0.20			3.63 (-3.42, 10.69)	0.31
General health (0-100)	10	1087	-0.03 (-0.26, 0.19)	0.79	10	1214	0.10 (-0.11, 0.30)	0.34
Mental health (0-100)	6	682	0.01 (-0.31, 0.32)	0.96	6	846	-0.05 (-0.20, 0.10)	0.53
Fear avoidance (0-100)	8	711	0.09 (-0.28, 0.46)	0.63	8	947	0.08 (-0.04, 0.20)	0.18
Social support								
No	10	1077	--	--	10	1273	--	--
Yes			3.58 (-4.05, 11.21)	0.36			-3.52 (-8.66, 1.63)	0.18
Episode duration (months)	13	1363	0.02 (-0.05, 0.09)	0.59	13	1408	0.02 (-0.05, 0.08)	0.58
Functional limitations (0-100)	24	2250	0.08 (-0.10, 0.27)	0.37	24	2657	-0.01 (-0.11, 0.10)	0.88

Pain intensity (0-100)	26	2463	-0.06 (-0.21, 0.09)	0.42	26	2846	-0.05 (-0.16, 0.07)	0.42
Any leg pain								
No	14	1482	--	--	14	1758	--	--
Yes			1.23 (-14.31, 16.77)	0.88			1.44 (-3.94, 6.82)	0.60
Any LBP medication use								
No	13	1275	--	--	13	1697	--	--
Yes			-2.11 (-14.72, 10.50)	0.74			-4.20 (-9.99, 1.59)	0.16

*An estimate for the interaction could not be obtained due to no participants in the comparison groups; LBP=low back pain.

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Appendix 7 (Table) – Functional Limitations Outcome, by Comparison Group Type. Treatment-variable interactions (adjusted results) on continuous functional limitations outcome (0-100), for exercise treatment relative to each of: A. no treatment/usual care and B. other conservative comparisons at follow-up time closest to 3 months. A negative interaction coefficient indicates decreased pain for the variable level (e.g. females) with exercise vs. each comparison type.

Variable	A. No treatment/usual care comparison				B. Other non-exercise conservative comparison			
	N studies	n participants	Interaction MD (95% CI)	p-value	N studies	n participants	Interaction MD (95% CI)	p-value
Age (years)	25	2363	0.13 (-0.07, 0.34)	0.21	25	2774	0.04 (-0.09, 0.17)	0.51
Sex								
Male	25	2363	--	--	25	2774	--	--
Female			-1.24 (-6.15, 3.67)	0.62			-1.96 (-5.05, 1.12)	0.21
High school education								
High school or less	10	860	--	--	10	1050	--	--
Beyond high school			0.30 (-6.86, 7.46)	0.93			-0.50 (-5.24, 4.25)	0.84
Current smoker								
No	9	1118	--	--	9	1314	--	--
Yes			0.50 (-7.19, 8.18)	0.90			-1.08 (-5.74, 3.58)	0.65
Regular physical activity								
No	12	1419	--	--	12	1615	--	--
Yes			-0.50 (-6.62, 5.62)	0.87			-0.85 (-5.02, 3.32)	0.69
BMI	15	1649	0.64 (0.04, 1.25)	0.04	15	1831	-0.24 (-0.72, 0.24)	0.33
History of LBP								
No	8	830	--	--	8	703	--	--
Yes			0.39 (-7.99, 8.77)	0.93			N/A*	N/A
Sick leave (past 12 months)								
No	13	1326	--	--	13	1357	--	--
Yes			1.51 (-6.99, 10.01)	0.73			-2.90 (-11.26, 5.45)	0.50
Work status								
Unemployed	17	1746	--	--	17	2167	--	--
Employed			-1.80 (-9.11, 5.50)	0.63			1.42 (-2.60, 5.44)	0.49
Heavy physical demands								
No	8	1209	--	--	8	1315	--	--
Yes			8.66 (-1.12, 18.45)	0.08			4.97 (-0.71, 10.64)	0.09
General health (0-100)	10	1101	-0.01 (-0.22, 0.21)	0.94	10	1255	-0.08 (-0.30, 0.14)	0.49
Mental health (0-100)	7	761	0.04 (-0.24, 0.32)	0.77	7	924	-0.03 (-0.21, 0.14)	0.70
Fear avoidance (0-100)	9	809	-0.01 (-0.29, 0.28)	0.97	9	1043	0.10 (0.002, 0.19)	0.05
Social support								
No	9	1005	--	--	9	1228	--	--
Yes			5.52 (-1.51, 12.55)	0.12			0.48 (-4.21, 5.17)	0.84
Episode duration (months)	13	1364	0.02 (-0.02, 0.06)	0.26	13	1408	0.13 (-11.67, 11.94)	0.98

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Functional limitations (0-100)	25	2363	-0.21 (-0.37, -0.05)	0.01	25	2774	-0.02 (-0.11, 0.07)	0.66
Pain intensity (0-100)	24	2286	0.06 (-0.05, 0.18)	0.30	24	2697	0.03 (-0.06, 0.11)	0.50
Any leg pain								
No	15	1589	--	--	15	1871	--	--
Yes			-6.41 (-19.57, 6.76)	0.34			0.91 (-3.33, 5.15)	0.67
Any LBP medication use								
No	13	1288	--	--	13	1716	--	--
Yes			-10.51 (-20.10, -0.92)	0.03			-3.82 (-7.92, 0.29)	0.07

*There were no participants in the comparison groups and an estimate for the interaction could not be obtained; LBP=low back pain.

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Appendix 8 (Table) – Global Recovery Outcome, by Comparison Group Type. Treatment-variable interactions (adjusted results) on important global recovery outcome (dichotomous), for exercise treatment relative to each of: A. no treatment/usual care and B. other conservative comparisons at follow-up time closest to 3 months. An interaction coefficient above 1 indicates increased likelihood of recovery for the variable level (e.g. females) with exercise vs. each comparison type.

Variable	A. No treatment/usual care comparison				B. Other non-exercise conservative comparison			
	N studies	n participants	Interaction OR (95% CI)	p-value	N studies	n participants	Interaction OR (95% CI)	p-value
Age (years)	25	2363	1.00 (0.97, 1.03)	0.82	25	2773	1.01 (0.99, 1.03)	0.37
Sex								
Male	25	2363	--	--	25	2773	--	--
Female			1.44 (0.71, 2.89)	0.31			1.32 (0.86, 2.03)	0.20
High school education								
High school or less	10	861	--	--	10	1050	--	--
Beyond high school			0.93 (0.37, 2.35)	0.88			1.53 (0.77, 3.02)	0.23
Current smoker								
No	9	1120	--	--	9	1315	--	--
Yes			0.40 (0.15, 1.08)	0.07			1.57 (0.76, 3.26)	0.22
Regular physical activity								
No	12	1420	--	--	12	1615	--	--
Yes			0.85 (0.38, 1.89)	0.70			0.98 (0.53, 1.81)	0.94
BMI	15	1652	0.87 (0.80, 0.95)	0.002	15	1833	0.99 (0.92, 1.07)	0.88
History of LBP								
No	8	830	--	--	8	703	--	--
Yes			1.05 (0.39, 2.78)	0.93			N/A*	N/A
Sick leave (past 12 months)								
No	13	1325	--	--	13	1356	--	--
Yes			1.40 (0.42, 4.65)	0.58			1.43 (0.51, 4.01)	0.49
Work status								
Unemployed	17	1745	--	--	17	2165	--	--
Employed			0.50 (0.19, 1.27)	0.14			1.14 (0.64, 2.00)	0.66
Heavy physical demands								
No	8	1211	--	--	8	1317	--	--
Yes			0.64 (0.16, 2.59)	0.53			0.51 (0.21, 1.22)	0.13
General health (0-100)	10	1100	1.00 (0.95, 1.04)	0.84	10	1253	1.01 (0.98, 1.05)	0.50
Mental health (0-100)	7	760	1.00 (0.91, 1.09)	0.98	7	922	0.99 (0.97, 1.01)	0.44
Fear avoidance (0-100)	9	806	1.01 (0.97, 1.06)	0.65	9	1039	1.00 (0.98, 1.01)	0.66
Social support								
No	9	1005	--	--	9	1227	--	--
Yes			0.79 (0.34, 1.82)	0.58			1.37 (0.74, 2.57)	0.32
Episode duration (months)	13	1367	1.00 (1.00, 1.01)	0.69	13	1410	1.00 (1.00, 1.01)	0.38

Functional limitations (0-100)	25	2363	1.00 (0.98, 1.03)	0.73	25	2773	1.01 (1.00, 1.02)	0.24
Pain intensity (0-100)	24	2289	1.00 (0.98, 1.01)	0.63	24	2699	1.00 (0.99, 1.02)	0.80
Any leg pain								
No	15	1590	--	--	15	1871	--	--
Yes			1.08 (0.19, 6.13)	0.93			1.02 (0.54, 1.91)	0.96
Any LBP medication use								
No	13	1288	--	--	13	1716	--	--
Yes			0.65 (0.20, 2.11)	0.47			1.95 (1.14, 3.34)	0.02

*There were no participants in the comparison groups and an estimate for the interaction could not be obtained; LBP=low back pain.

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