

SUPPLEMENTAL MATERIAL

Modulation of cardiac fatty acid or glucose oxidation to treat heart failure in preclinical models: A systematic review and meta-analysis

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Ovid Medline – 03/02/2024

Ovid MEDLINE(R) ALL <1946 to March 02, 2024>

1 (exp Heart/ or heart.tw. or exp Myocardium/ or myocard*.tw. or exp Myocytes, Cardiac/ or
 2 cardiomyocyte*.tw. or exp Heart Ventricles/ or left ventric*.tw. or exp Ventricular Function/ or
 3 (ventric* adj3 function*).tw. or (cardi* adj3 function*).tw. or exp Heart Diseases/ or exp Heart Injuries/
 4 or exp Cardiomyopathy/ or cardiomyopath*.tw. or exp Heart Failure/ or (cardi* adj3 fail*).tw. or exp
 5 Ventricular Dysfunction/ or (cardi* adj3 dysfunction*).tw.) and (fat* oxid* or fat* acid* oxid* or beta
 6 oxid* or FA-Oxid* or FA-Metabolism or Palmit* Oxid* or Olea* Oxid* or Fat* acid* metabolism or
 7 carbohydrat* oxid* or glucose oxid* or pyruvate oxid* or glucose metabolism or metabolic
 8 modulat*).tw.

Web of Science – 03/02/2024

1 ((TI=(heart) OR TI= (myocard*) OR TI=(cardiomyocyte*) OR TI=(left ventric*) OR
 2 TI=(cardiomyopath*) OR TI=(cardi* NEAR/3 fail*) OR TI=(cardi* NEAR/3 function*) OR
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 4 dysfunction*)) AND (TI=("fat* acid* oxid*") OR TI=("fat* oxid*") OR TI=("beta oxid*") OR
 5 TI=("FA oxid*") OR TI=("FA Metabolism") OR TI=("Palmit* Oxid*") OR TI=("Olea* Oxid*") OR
 6 TI=("Fat* acid* metabolism*") OR TI=("carbohydrat* oxid*") OR TI=("glucose oxid*") OR
 7 TI=("pyruvate oxid*") OR TI=("glucose metabolism") OR TI=("metabolic modulat*")) OR
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 11 dysfunction*)) AND (AB=("fat* acid* oxid*") OR AB=("fat* oxid*") OR AB=("beta oxid*") OR

1 AB=("FA oxid*") OR AB=("FA Metabolism") OR AB=("Palmit* Oxid*") OR AB=("Olea* Oxid*")
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3 AB=("pyruvate oxid*") OR AB=("glucose metabolism") OR AB(("metabolic modulat*"))
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5 Scopus - 03/02/2024
6 TITLE-ABS ((heart OR myocard* OR cardiomyocyte* OR (left AND ventric*) OR cardiomyopath*
7 OR (cardi* W/3 fail*) OR (cardi* W/3 function*) OR (ventric* W/3 function*) OR (cardi* W/3
8 dysfunction*) OR (ventric* W/3 dysfunction*)) AND ("fat* oxid*" OR "fat* acid* oxid*" OR "beta
9 oxid*" OR "FA-Oxid*" OR "FA-Metabolism" OR "Palmit* Oxid*" OR "Olea* Oxid*" OR "Fat* acid*
10 metabolism" OR "carbohydrate* oxid*" OR "glucose oxid*" OR "pyruvate oxid*" OR "glucose
11 metabolism" OR "metabolic modulat*"))

Metabolic Change	Estimate	p-value	t-value	df	95% Confidence interval
FAO↑	1.04	7.28×10^{-5}	4.41	41	0.56 - 1.52
FAO↓	0.21	0.696	0.39	29	-0.86 - 1.27
GO↑	1.08	2.94×10^{-13}	8.31	109	0.82 - 1.34
GO↑FAO↓	0.44	0.051	4.58	44	-0.00 - 0.89
GO↓FAO↑	-0.06	0.889	-0.41	47	-0.92 - 0.80

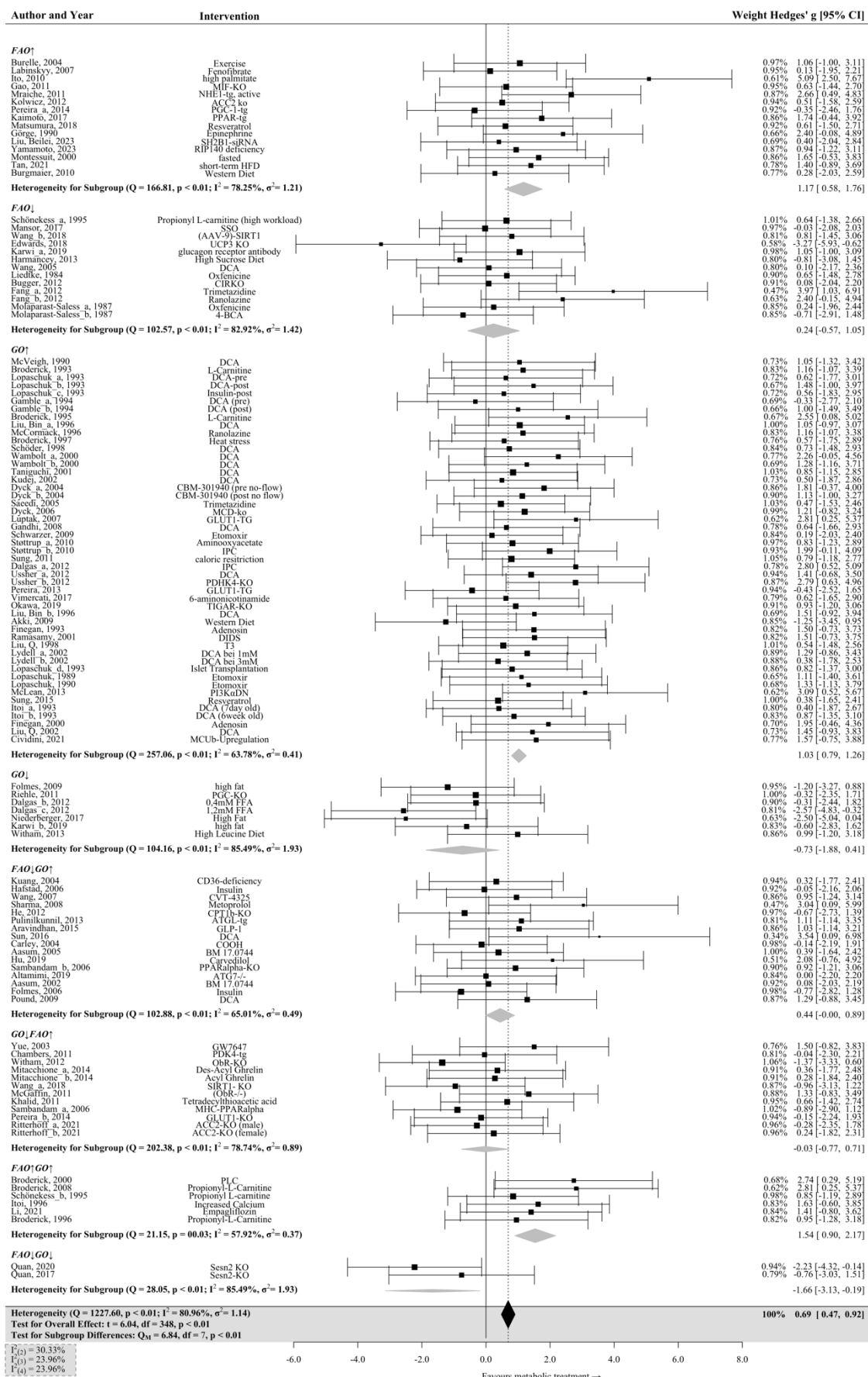
Supplementary Table 1: Subgroup analysis for studies with rodents.

Estimates presented as Hedges' g. Results of multivariate meta-analysis when only rodent animals are considered. FAO: fatty acid oxidation, GO: glucose oxidation, ↑ or ↓: increased or decreased, df: degrees of freedom

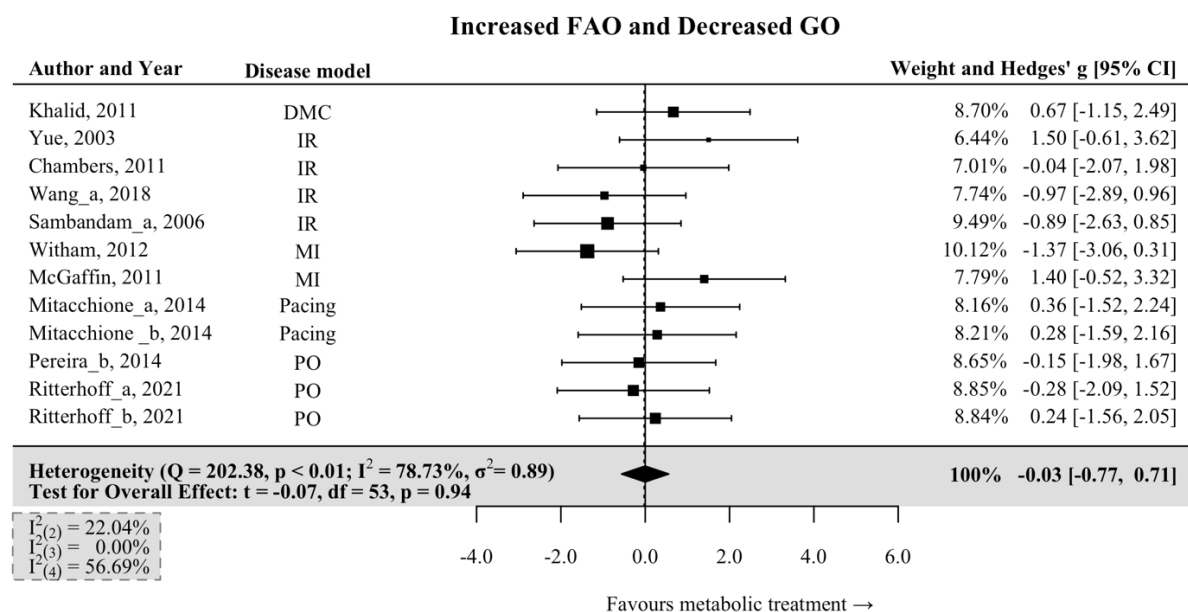
Metabolic Change	Intercept	p-value	t-value	df	95% Confidence interval
FAO↑	1.61	0.322	1.00	45	0.54 - 2.68
FAO↓	-0.12	0.434	0.79	35	-1.34 - 1.10
GO↑	0.89	0.504	0.67	113	0.40 - 1.37
GO↑FAO↓	-0.83	4.00×10^{-5}	4.58	43	-1.39 to -0.274
GO↓FAO↑	0.28	0.661	0.44	52	-1.69 - 1.12

Supplementary Table 2: Regression test for funnel plot asymmetry.

FAO: fatty acid oxidation, GO: glucose oxidation, ↑ or ↓: increased or decreased, df: degrees of freedom

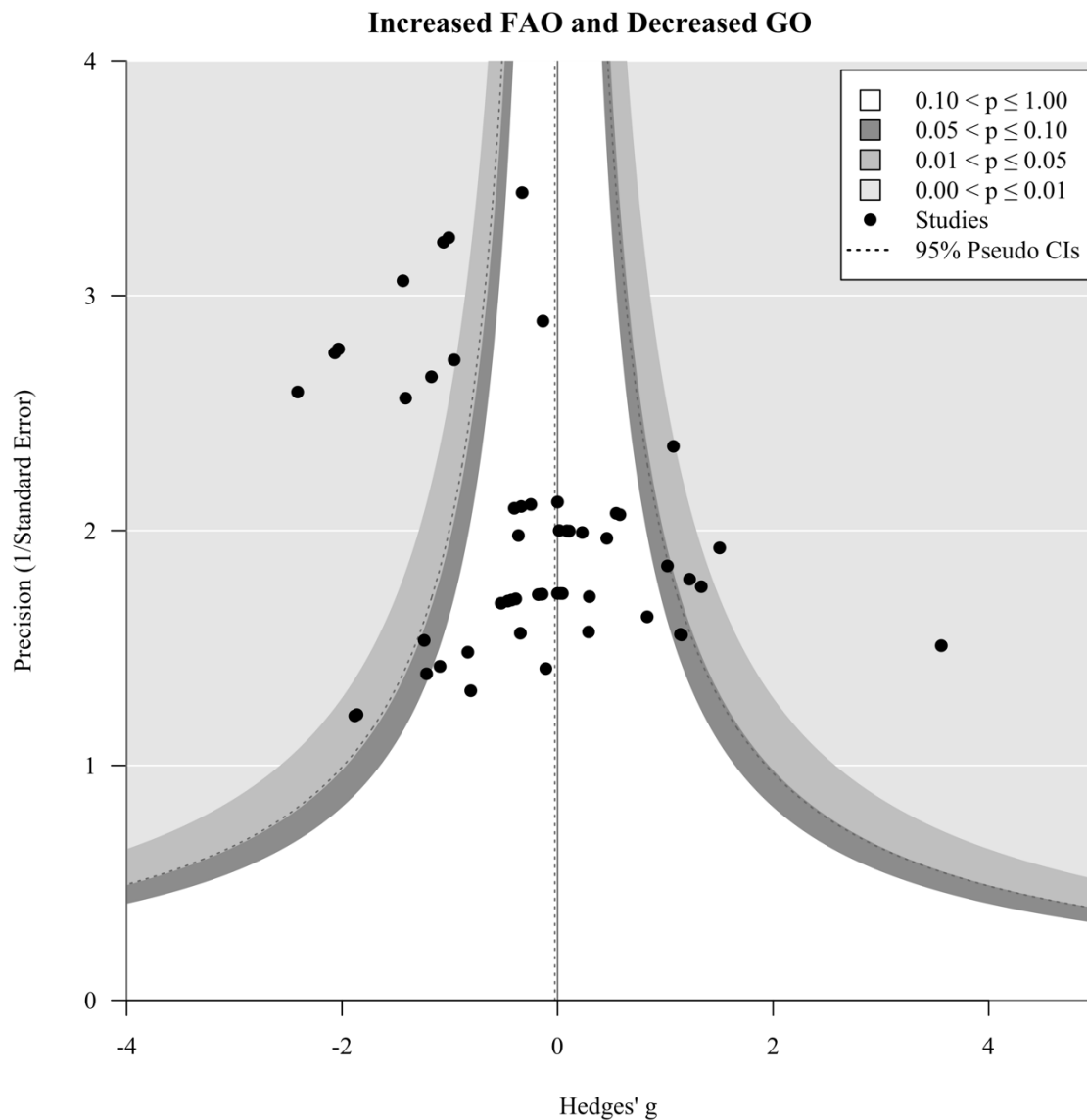


Supplementary Figure 1: Forest plot of all included studies¹⁻¹⁰³. Grouped by metabolic change. Data are presented as Hedges' g, which is calculated using multivariate meta-analysis to enclose all measures of heart function reported in each study. Bars represent 95% CI. Tests for the overall effect and confidence intervals are based on the Knapp and Hartung method. Individual box sizes are determined by their weight in the meta-analysis model. Number of control (n = 1027) and intervention group (n = 995) animals. The components of heterogeneity across levels are quantified by partitioned I^2 -statistics: (2) between-outcomes; (3) between-interventions; (4) between studies. FAO: fatty acid oxidation, GO: glucose oxidation, ↑ or ↓: increased or decreased.

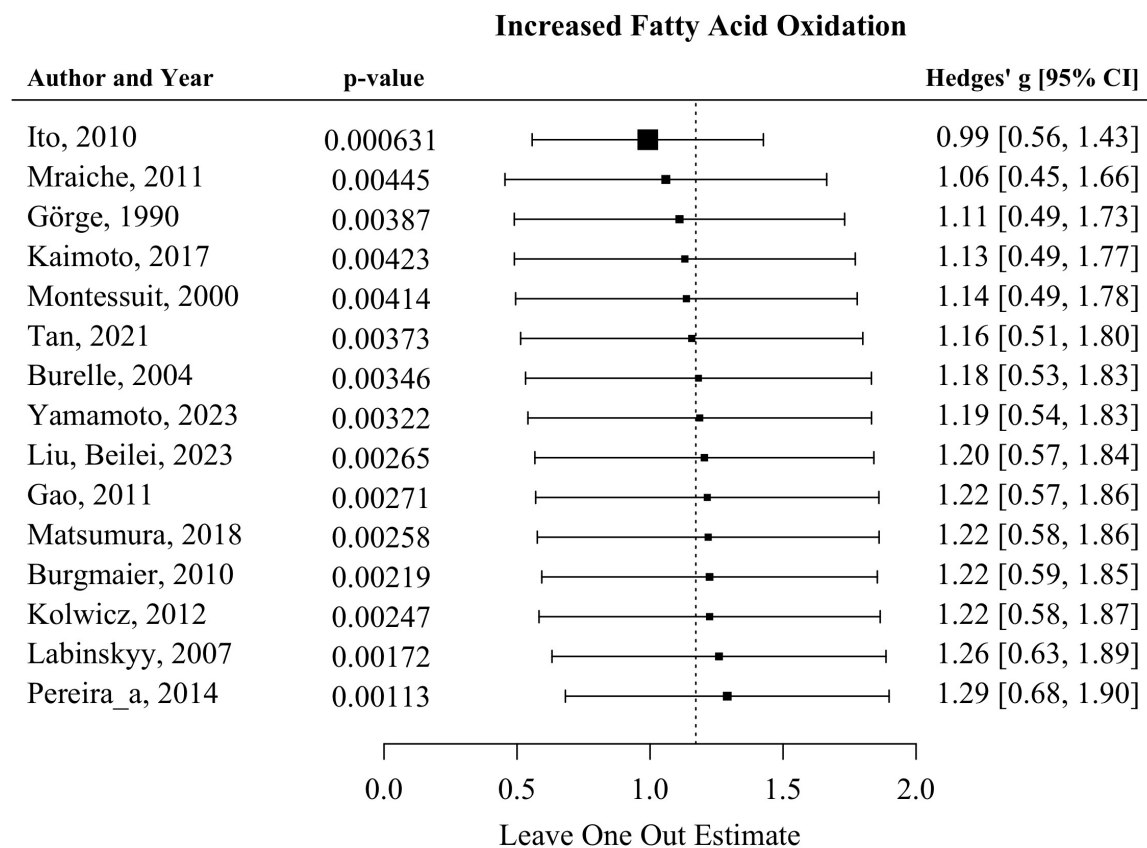


Supplementary Figure 2: Forest plot of interventions associated with increased cardiac fatty acid oxidation and decreased cardiac glucose oxidation (FAO↑GO↓). Data are presented as Hedges' g, which is calculated using a multivariate meta-analysis to enclose all measures of heart function reported in each study. Bars represent 95% CI. Tests for the overall effect and confidence intervals are based on the Knapp and Hartung method. Individual box sizes are determined by their weight in the meta-analysis model. Number of control and (n = 96) intervention group (n = 100) animals. The components of heterogeneity across levels are quantified by partitioned I^2 -statistics: (2) between-outcomes; (3)

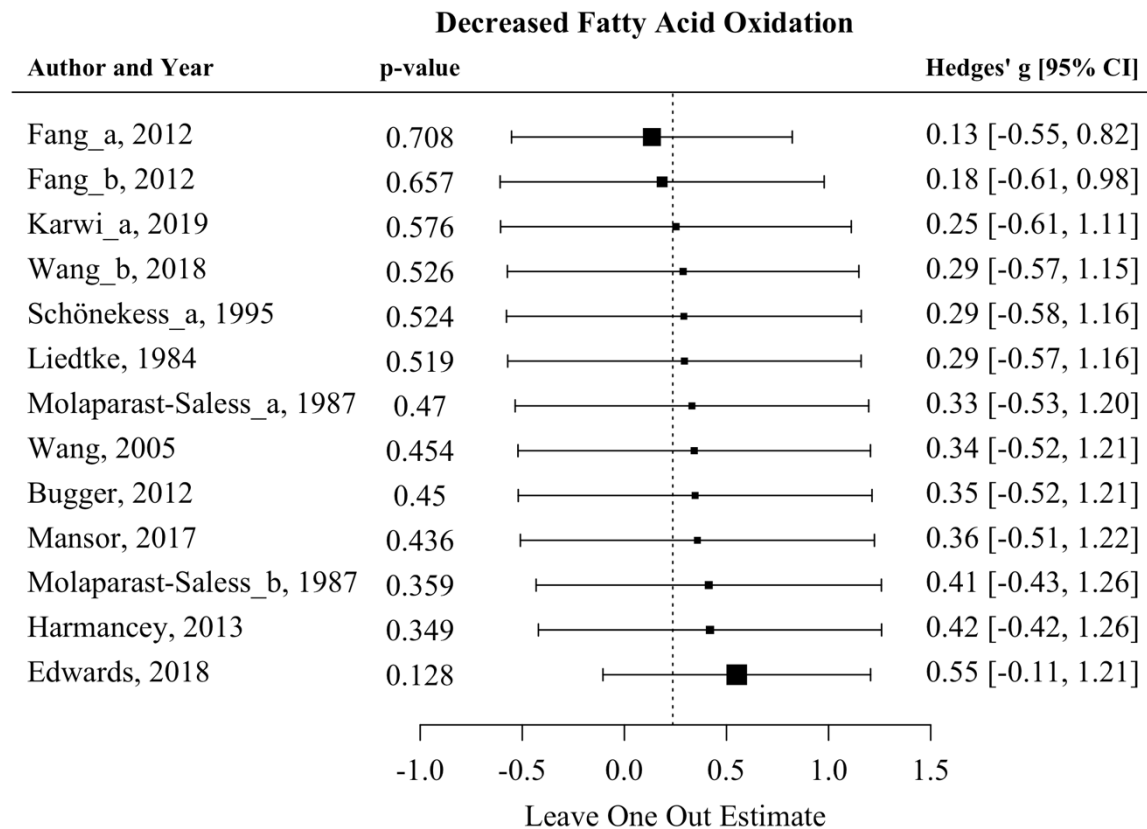
between-interventions; (4) between studies. IR: ischemia-reperfusion, PO: pressure overload, MI: myocardial infarction, DMC: diabetic cardiomyopathy, Pacing: pacing-induced heart failure.



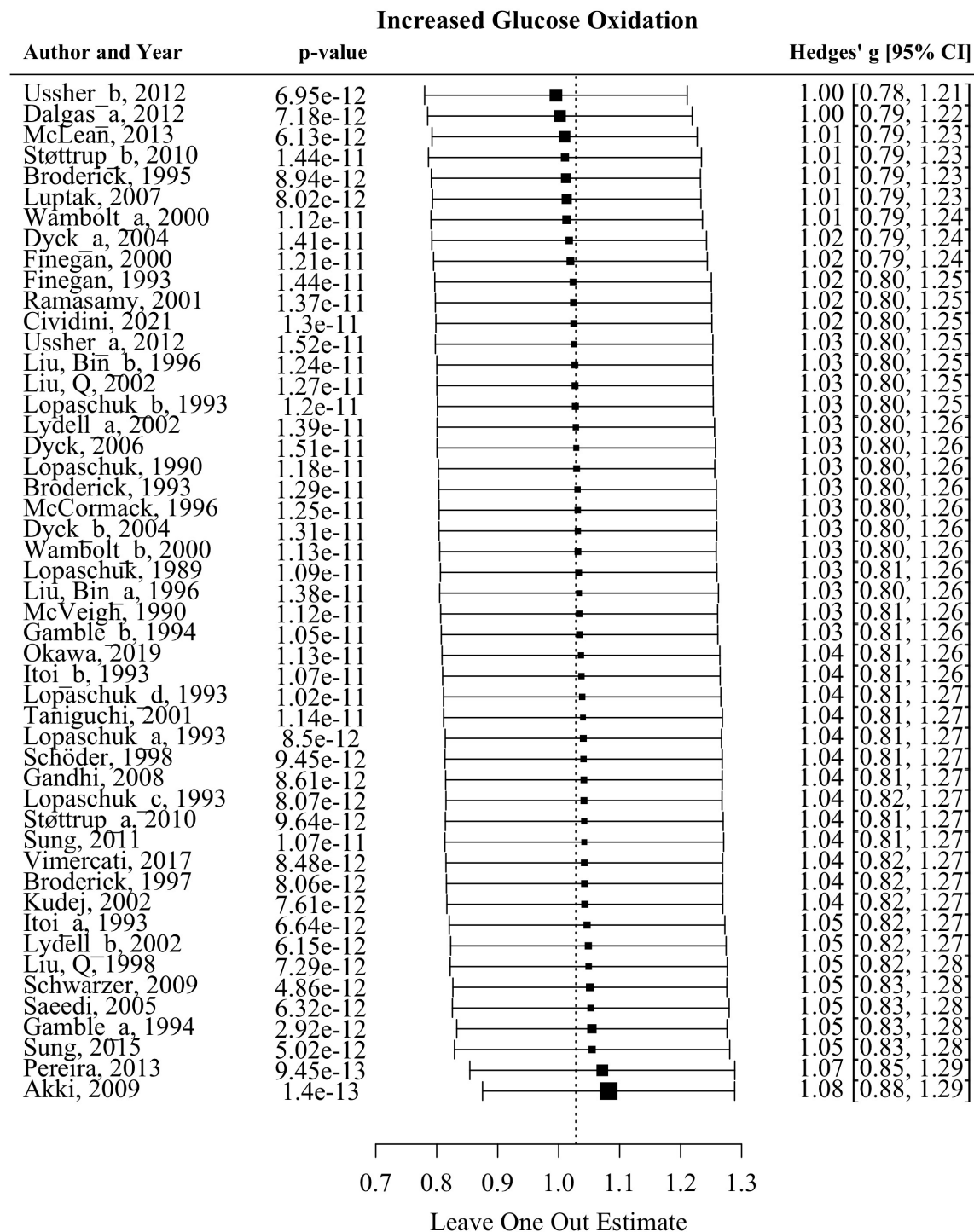
Supplementary Figure 3: Contour-enhanced funnel plot of interventions associated with increased cardiac fatty acid oxidation and decreased cardiac glucose oxidation (FAO↑GO↓). The plot shows the observed effect sizes against the corresponding inverse standard errors. Contours of significance are centered around null, and dotted pseudo 95% confidence interval (CI) guidelines are depicted around the random-effects pooled estimate.



Supplementary Figure 4: Leave-one-out forest plot for interventions associated with increased cardiac fatty acid oxidation (FAO $\uparrow$). For each study, the effect size displayed corresponds to an overall effect size calculated from a meta-analysis excluding that study. A vertical line at the overall effect size based on the complete set of studies (with no omission) is plotted to help detect influential studies. Data are presented as Hedges' g. Bars represent 95% CI. Tests for the overall effect and confidence intervals are based on the Knapp and Hartung method. Individual box sizes are determined by their weight in the meta-analysis model. Number of control (n = 127) and intervention group (n = 133) animals.

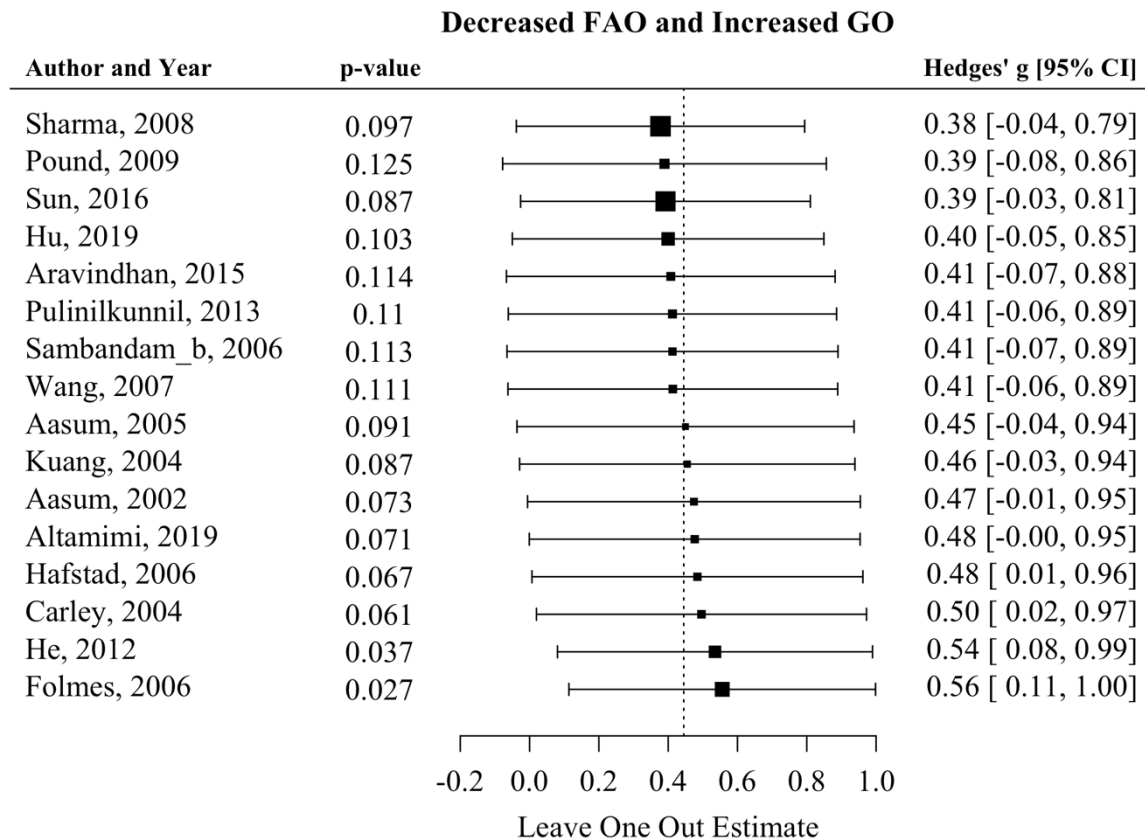


Supplementary Figure 5: Leave-one-out forest plot for interventions associated with decreased cardiac fatty acid oxidation (FAO↓). For each study, the effect size displayed corresponds to an overall effect size calculated from a meta-analysis excluding that study. A vertical line at the overall effect size based on the complete set of studies (with no omission) is plotted to help detect influential studies. Data are presented as Hedges' g. Bars represent 95% CI. Tests for the overall effect and confidence intervals are based on the Knapp and Hartung method. Individual box sizes are determined by their weight in the meta-analysis model. Number of control (n = 92) and intervention group (n = 88) animals.

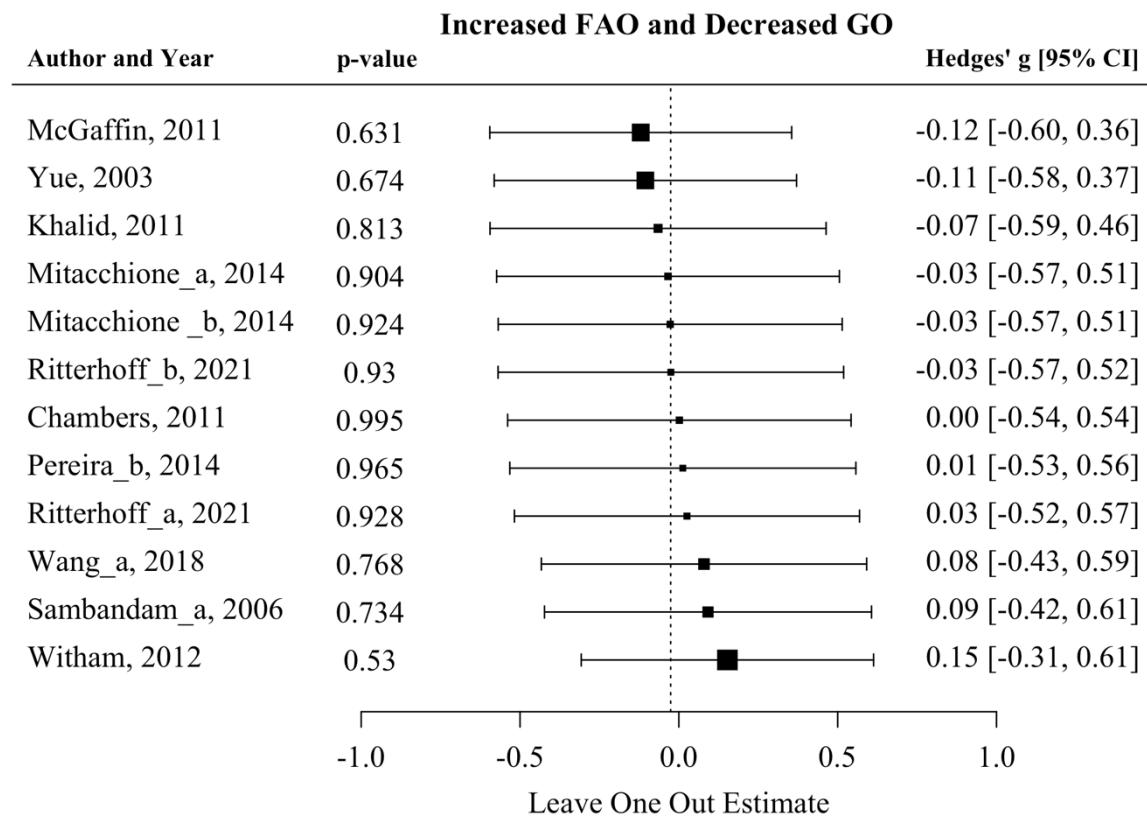


Supplementary Figure 6: Leave-one-out forest plot for interventions associated with increased cardiac glucose oxidation (GO↑). For each study, the effect size displayed corresponds to an overall effect size calculated from a meta-analysis excluding that study. A vertical line at the overall effect size based on the complete set of studies (with no omission) is plotted to help detect influential studies. Data

are presented as Hedges' g . Bars represent 95% CI. Tests for the overall effect and confidence intervals are based on the Knapp and Hartung method. Individual box sizes are determined by their weight in the meta-analysis model. Number of control ($n = 393$) and intervention group ($n = 418$) animals.



Supplementary Figure 7: Leave-one-out forest plot for interventions associated with decreased cardiac fatty acid oxidation and increased glucose oxidation (FAO↓GO↑). For each study, the effect size displayed corresponds to an overall effect size calculated from a meta-analysis excluding that study. A vertical line at the overall effect size based on the complete set of studies (with no omission) is plotted to help detect influential studies. Data are presented as Hedges' g. Bars represent 95% CI. Tests for the overall effect and confidence intervals are based on the Knapp and Hartung method. Individual box sizes are determined by their weight in the meta-analysis model. Number of control (n = 147) and intervention group (n = 147) animals.



Supplementary Figure 8: Leave-one-out forest plot for interventions associated with increased cardiac fatty acid oxidation and decreased glucose oxidation (FAO↑GO↓). For each study, the effect size displayed corresponds to an overall effect size calculated from a meta-analysis excluding that study. A vertical line at the overall effect size based on the complete set of studies (with no omission) is plotted to help detect influential studies. Data are presented as Hedges' g. Bars represent 95% CI. Tests for the overall effect and confidence intervals are based on the Knapp and Hartung method. Individual box sizes are determined by their weight in the meta-analysis model. Number of control and (n = 96) intervention group (n = 100) animals.

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