Supplemental Material

Relation of Insulin Resistance to Brain Glucose Metabolism in Fasting and Hyperinsulinemic States: A Systematic Review and Meta-Analysis

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Supplemental Table S1. Specific search terms used in each database

Database: PubMed

((“fluorodeoxyglucose f18”[MeSH] OR “fdg”[Journal] OR “fdg”[All Fields] “cmrg*”[All Fields] OR ”Cerebral glucose metabolism”[All Fields] OR ”Brain glucose uptake”[All Fields])

AND

(“diabetes mellitus, type 2”[MeSH] OR “overweight”[MeSH] OR “Polycystic ovary syndrome”[MeSH] OR “metabolic syndrome”[MeSH] OR “Insulin resistance”[MeSH] OR “Type 2 diabetes”[All Fields] OR (“obeses”[All Fields] OR "obesity"[MeSH] OR "obesity"[All Fields] OR "obese" [All Fields] OR "obesities" [All Fields] OR "obesity s" [All Fields])OR ("overweight" [MeSH] OR "overweight" [All Fields] OR "overweighted" [All Fields]” OR "overweightedness" [All Fields] OR "overweights" [All Fields] OR Polycystic ovary syndrome”[All Fields] OR “Polycystic ovarian syndrome”[All Fields] OR "PCOS"[All Fields] OR ”Metabolic syndrome”[All Fields] OR “Insulin resistance”[All Fields] OR ("prediabetic state" [MeSH] OR ("prediabetic" [All Fields] AND "state" [All Fields]) OR "prediabetic state" [All Fields] OR "prediabetes" [All fields] OR "prediabetics" [All Fields]) OR “Insulin sensitivity”[All fields] OR ”impaired glucose tolerance”[All Fields] OR ”impaired fasting glucose”[All Fields]))

AND

("Brain" [MeSH] OR "Brain" [All Fields] OR "Brains" [All Fields], OR "brain s" [All Fields] OR "cerebrally" [All Fields] OR "cerebrum" [MeSH] OR "cerebrum" [All Fields] OR "cerebral[All Fields]")

Database: Embase

('exp Fluorodeoxyglucose f 18/' OR 'FDG.mp' OR 'cerebral glucose metabolism.mp' OR 'brain glucose uptake.mp' OR 'CMRg*.mp')

AND

('exp non insulin dependent diabetes mellitus/' OR 'Type 2 diabetes.mp.' OR 'exp obesity/' OR 'Obesity.mp.' OR 'Overweight.mp.' OR 'exp ovary polycystic disease/' OR 'Polycystic ovary syndrome.mp.' OR Polycystic ovarian syndrome.mp.' OR 'PCOS.mp.' OR 'Exp metabolic syndrome X/' OR 'Metabolic syndrome.mp.' OR 'Exp insulin resistance/' OR 'insulin resistance.mp.' OR 'Prediabetes.mp.' OR 'exp insulin sensitivity/' OR 'insulin sensitivity.mp.' OR 'exp impaired glucose tolerance/' OR 'impaired glucose tolerance.mp.' OR 'impaired fasting glucose.mp.')

AND

('exp brain/' OR 'Cerebral.mp.' OR 'brain.mp.')

Database: CENTRAL

("Fluorodeoxyglucose F18"[MeSH] OR FDG[All text] OR CMRg*[All text] OR "Cerebral glucose metabolism"[All text] OR "Brain glucose uptake"[All text])

AND

("Diabetes Mellitus, Type 2"[MeSH] OR "Type 2 diabetes"[All text] OR "Overweight"[MeSH] OR Overweight[All text] OR Obesity[All text] OR "Polycystic Ovary Syndrome"[MeSH] OR "Polycystic ovary syndrome"[All text] OR "Polycystic ovarian syndrome"[All text] OR PCOS[All text] OR "Metabolic syndrome"[MeSH] OR "Metabolic syndrome"[All text] OR "Insulin resistance"[MeSH] OR "Insulin resistance"[All text] OR Prediabetes[All text] OR "Insulin sensitivity"[All text] OR "Impaired glucose tolerance"[All text] OR "Impaired fasting glucose"[All text])

AND

("Brain"[MeSH] OR Brain[All text] OR Cerebral[All text])

Note: The argument ‘explode all trees’ was applied for all [MeSH] terms. In [All text] arguments word variations have been searched.

Database: Web of Science

((((ALL=(“Flourodeoxyglucose F18”)) OR ALL=(FDG)) OR ALL=(CMRg*))
OR ALL=(”cerebral glucose metabolism”)) OR ALL=(”brain glucose uptake”)

AND

((((((((((ALL=("Type 2 diabetes")) OR ALL=(Overweight)) OR ALL=(Obesity)) OR ALL=(”Polycystic ovary syndrome”)) OR ALL=(“Polycystic ovarian syndrome”)) OR ALL=(PCOS)) OR ALL=(”Metabolic syndrome”)) OR ALL=(“Insulin resistance”)) OR ALL=(Prediabetes)) OR ALL=(“Insulin sensitivity”)) OR ALL=(”impaired glucose tolerance”)) OR ALL=(”impaired fasting glucose”)

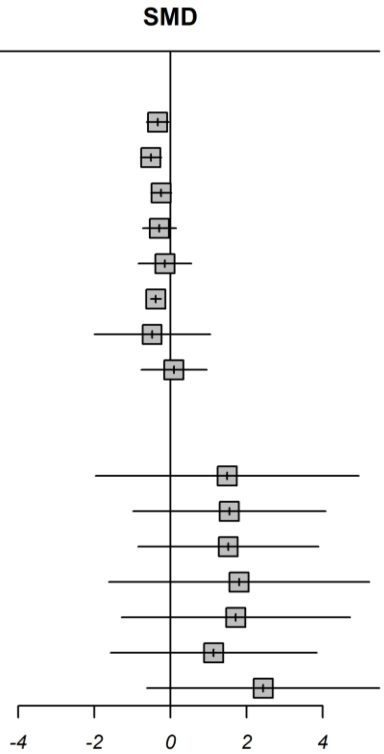
AND

(ALL=(Brain)) OR ALL=(Cerebral)

Note: All searches were conducted on February 24th, 2022.

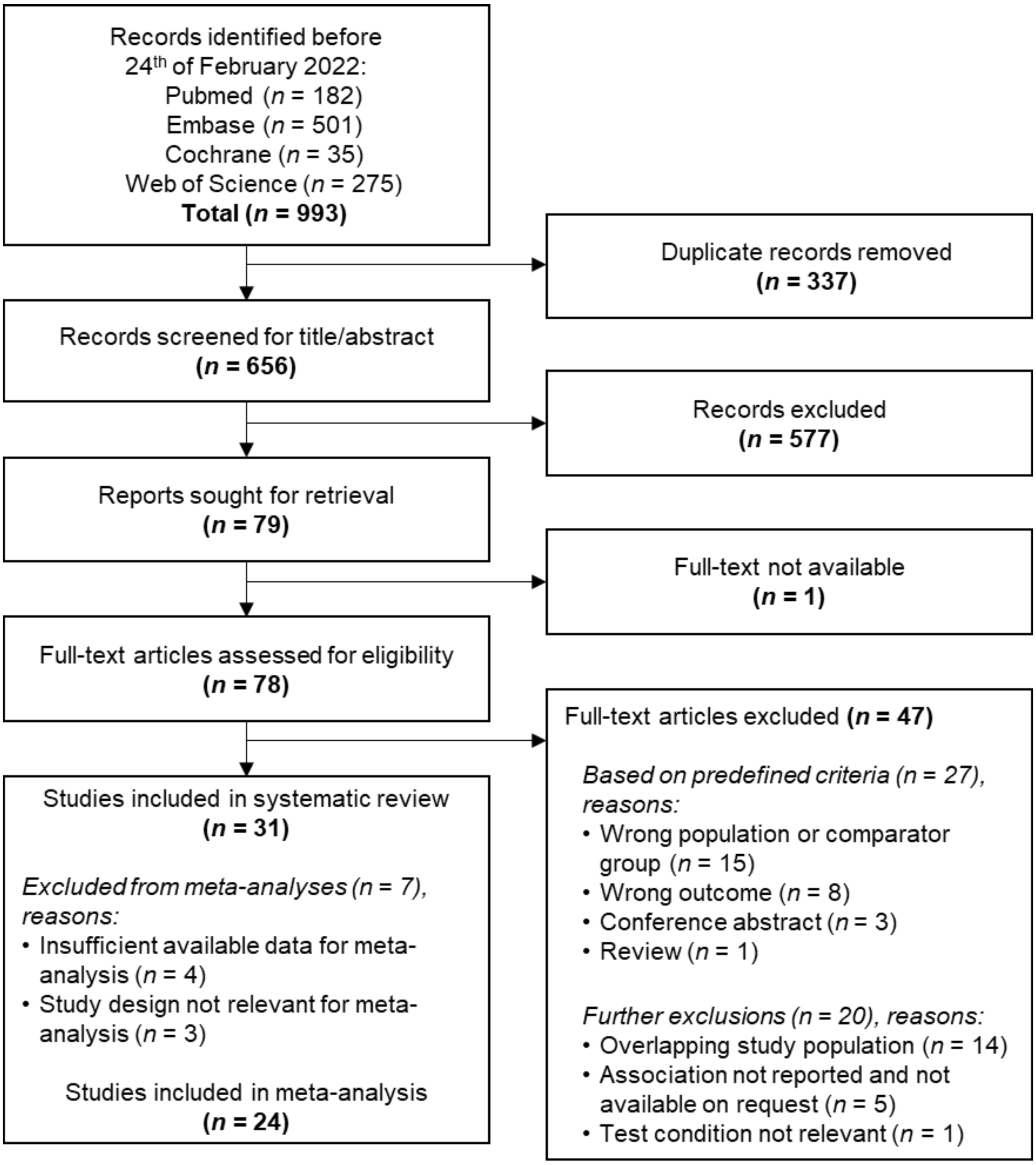
Supplemental Fig. S1. Forest plot of brain regions stratified by metabolic condition (fasting vs insulin stimulation)

Brain regions	Number of studies	Interaction P-value	Hedges' g [95%-CI]
Fasting			
Whole brain	12	0.56	-0.33 [-0.62; -0.04]
Frontal	14		-0.51 [-0.78; -0.24]
Temporal	8		-0.24 [-0.51; 0.03]
Parietal	10		-0.29 [-0.73; 0.15]
Occipital	5		-0.14 [-0.84; 0.55]
Subcortical	9		-0.38 [-0.52; -0.25]
Cingulate	3		-0.48 [-2.00; 1.04]
Cerebellum	5		0.09 [-0.77; 0.95]
Hyperinsulinemic clamp			
Whole brain	2	0.76	1.49 [-1.96; 4.95]
Frontal	3		1.55 [-0.98; 4.08]
Temporal	3		1.52 [-0.85; 3.89]
Parietal	3		1.81 [-1.61; 5.22]
Occipital	3		1.72 [-1.29; 4.72]
Subcortical	2		1.14 [-1.57; 3.84]
Cerebellum	4		2.44 [-0.62; 5.49]



Note: Summary of standardized mean differences of brain glucose metabolism within each selected brain region. Reports from insula, midbrain and pons were excluded due to low study numbers.

Supplemental Fig. S2. Flow chart of study inclusion



Supplemental Table S1. Overview of excluded reports during full-text screening.

Studies excluded from systematic review
Reason: Wrong population or comparator group: (1-15) Reason: Wrong outcome: (16-23) Reason: Conference abstract: (24-26) Reason: Review: (27) *Further exclusions* Reason: Overlapping study population: · Li 2016: (28-33) · Eriksson 2021: (34; 35) · Garcia-Casares 2014: (36) · Képes 2021: (37) · Reports including pooled data: (38-41) Reason: Association not reported and not available on request: (42-46) Reason: Test condition not relevant: (47)
Studies excluded from meta-analysis
Reason: Insufficient available data for meta-analysis: (48-51) Reason: Study design not relevant for meta-analysis: (52-54)

Note: References are found at the end of the supplemental material.

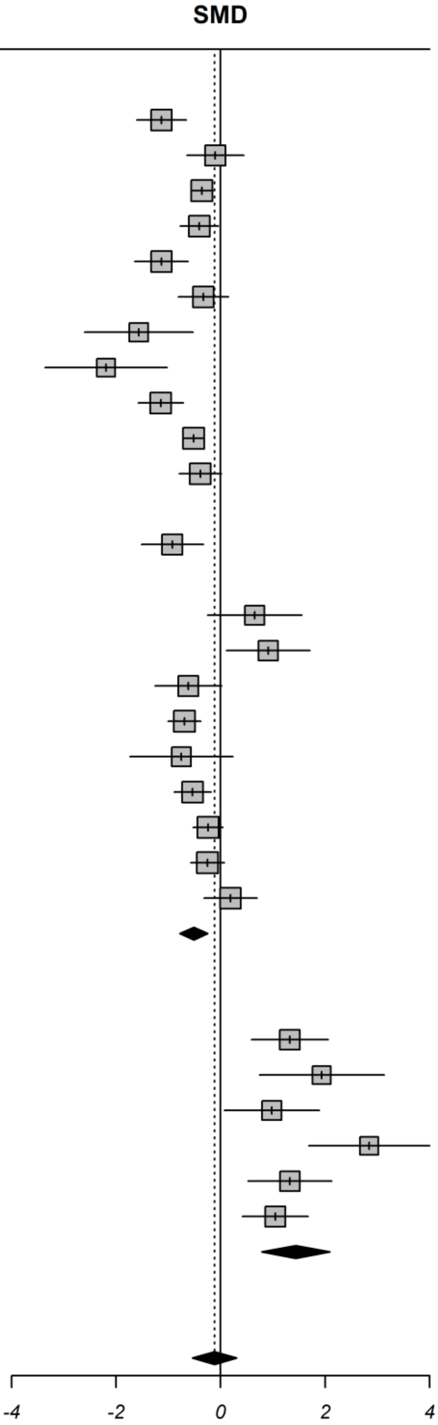
Supplemental Table S3. Quality assessment of included studies in the meta-analysis

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Risk
Baker, 2011	🟢	🟢	🟢	🟢	🟢	🔴	🔴	🟢	Low
Büsing, 2013	🟢	🟢	🟡	🟡	🟢	🔴	🔴	🟢	Moderate
Castellano, 2015	🟢	🔴	🟢	🟢	🟢	🟢	🟢	🔴	Low
Chen, 2022	🟢	🟢	🟢	⚪	🟢	🟢	🔴	🟢	Low
Eriksson, 2021	🟢	🔴	🟢	🟢	🟢	🟢	🟢	🟢	Low
Femminella, 2021	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Low
GarcÃ-a-Casares, 2014	🟢	🟢	🟢	🟢	🟢	🔴	🔴	🟢	Low
Hirvonen, 2011	🔴	🔴	🟢	🟢	🟢	🔴	🟢	🟢	Moderate
Honkala, 2018	🟢	🟢	🟢	🟡	🟢	🔴	🟢	🟢	Low
Ishibashi, 2015	🟢	🔴	🟢	🟢	🔴	🔴	🔴	🟢	Moderate
Ishibashi, 2017	🟢	🔴	🟢	⚪	🟢	🟢	🔴	🟢	Moderate
Képes, 2021	🟢	🟢	🟡	🟡	🟢	🔴	🔴	🟢	Moderate
Latva-Rasku 2018	🟢	🟢	🟡	⚪	🟢	🟢	🟢	🟢	Low
Li, 2016	🟢	🟢	🟡	🟡	🟢	🟢	🔴	🟢	Moderate
Li, 2022	🟢	🟢	🟢	🟢	🟢	🟢	🔴	🟢	Low
Nam, 2017	🟢	🟢	🟢	🟢	🟢	🔴	🔴	🟢	Low
Nummenmaa, 2012	🟢	🔴	🟡	🟡	🟢	🟢	🟢	🟢	Moderate
Orava, 2014	🔴	🔴	🟢	🟢	🟢	⚪	🟢	🟢	Moderate
Roberts, 2014	🟢	🟢	🟡	🟡	🟢	🟢	🔴	🟢	Moderate
Tuulari, 2013	🟢	🟢	🟢	🟢	🟢	⚪	🟢	🟢	Low
Wang, 2001	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟡	Low
Wang, 2002	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	Low
Waqas, 2019	🟢	🟢	🟢	🟢	🟢	🔴	🔴	🟢	Low
Willette, 2015	🟢	🟢	🟢	⚪	🟢	🟢	🔴	🟢	Low

The Joanna Briggs Institute (JBI) Critical Appraisal tool for Analytical Cross-Sectional studies was used for quality assessment. Q1: Were the criteria for inclusion in the sample clearly defined? Q2: Were the study subjects and the setting described in detail? Q3: Was the exposure measured in a valid and reliable way? Q4: Were objective, standard criteria used for measurement of the condition? Q5: Were confounding factors identified? Q6: Were strategies to deal with confounding factors stated? Q7: Were the outcomes measured in a valid and reliable way? Q8: Was appropriate statistical analysis used? Questions were answered by 'yes' 🟢, 'no' 🔴, 'unclear' 🟡, or 'not applicable' ⚪. Scoring was based on Yes-answers, and <50%, 50-69%, ≥70% were considered as 'High', 'Moderate', and 'Low' risk studies, respectively. In Q2 a lack of recruitment period description was not considered sufficient to score as 'no'. In most studies exposure and condition (Q3 and Q4) were identical. In Q5 and Q6 age, sex, and BMI were considered important confounders. Q7 was only registered as 'yes' if a quantitative methodology was applied.

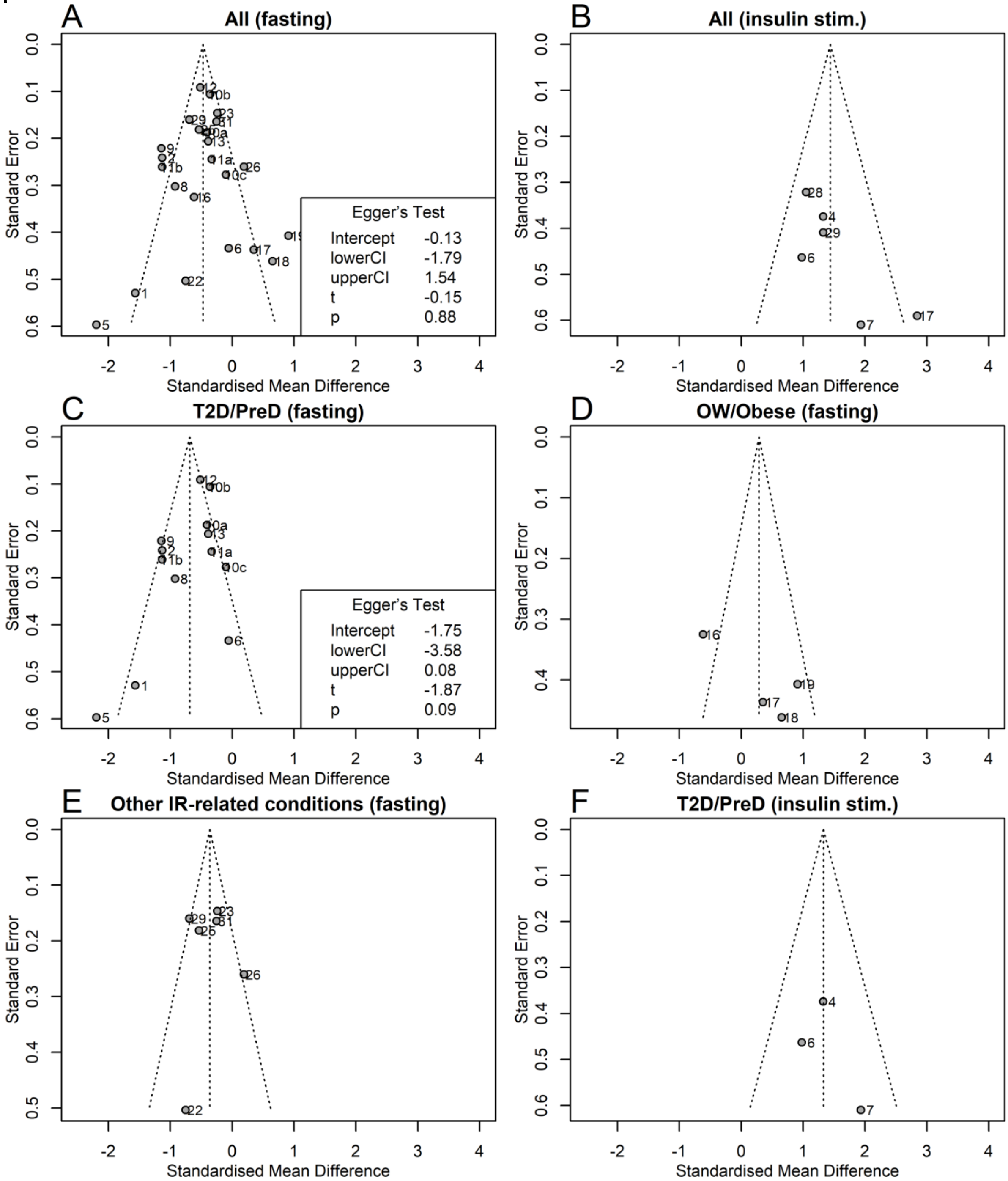
Supplemental Fig. S3. Forest plot of all 24 studies stratified by metabolic condition (fasting vs insulin stimulation)

Author, year (study population)	Total N	Hedges' g [95%-CI]
Fasting		
Busing, 2013 (T2D)	*90*	*-1.13 [-1.60; -0.66]*
Li, 2016 (T2D, AD)	*203*	*-0.10 [-0.64; 0.44]*
Li, 2016 (T2D, MCI)	*1034*	*-0.36 [-0.57; -0.15]*
Li, 2016 (T2D, CH)	*429*	*-0.41 [-0.77; -0.04]*
Li, 2022 (T2D, elderly)	*69*	*-1.13 [-1.64; -0.62]*
Li, 2022 (T2D, middleage)	*68*	*-0.33 [-0.81; 0.15]*
Baker, 2011 (T2D/PreD)	*23*	*-1.56 [-2.60; -0.53]*
Garcia-Casares, 2014 (T2D/PreD)	*25*	*-2.19 [-3.36; -1.02]*
Kepes, 2021 (T2D/PreD)	*96*	*-1.14 [-1.58; -0.71]*
Roberts, 2014 (T2D/PreD)	*749*	*-0.52 [-0.70; -0.34]*
Waqas, 2019 (T2D/PreD)	*119*	*-0.39 [-0.79; 0.02]*
Hirvonen, 2011 (IGT)	*22*	*-0.05 [-0.90; 0.80]*
Ishibashi, 2015b (IFG)	*51*	*-0.92 [-1.51; -0.33]*
Tuulari, 2013 (morbidly obese, incl.T2D/PreD)	*29*	*0.35 [-0.50; 1.21]*
Wang, 2001 (morbidly obese)	*20*	*0.65 [-0.25; 1.56]*
Wang, 2002 (morbidly obese)	*30*	*0.91 [0.11; 1.71]*
Orava, 2014 (OW/Obese)	*41*	*-0.62 [-1.25; 0.02]*
Nam, 2017 (MetS)	*264*	*-0.69 [-1.01; -0.38]*
Castellano, 2015 (PCOS)	*18*	*-0.75 [-1.74; 0.24]*
Femminella, 2021 (AD)	*130*	*-0.54 [-0.89; -0.18]*
Chen, 2022 (CH, incl. T2D 13%)	*189*	*-0.24 [-0.53; 0.05]*
Willette, 2015 (older middle-aged, CH)	*150*	*-0.25 [-0.57; 0.07]*
Ishibashi, 2017 (NW, CH)	*59*	*0.19 [-0.32; 0.70]*
Total (95% CI)		**-0.51 [-0.78; -0.25]**
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 72.42$, df = 20 (P < 0.001); $I^2 = 72\%$		
Hyperinsulinemic clamp		
Eriksson, 2021 (T2D/PreD)	*41*	*1.33 [0.59; 2.06]*
Honkala, 2018 (T2D/PreD)	*21*	*1.94 [0.74; 3.13]*
Hirvonen, 2011 (IGT)	*22*	*0.98 [0.07; 1.89]*
Tuulari, 2013 (morbidly obese, incl.T2D/PreD)	*29*	*2.84 [1.69; 4.00]*
Nummenmaa, 2012 (morbidly obese)	*30*	*1.33 [0.52; 2.13]*
Latva-Rasku, 2018 (p.P50T/AKT2 carriers)	*45*	*1.05 [0.42; 1.68]*
Total (95% CI)		**1.44 [0.79; 2.09]**
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 8.83$, df = 5 (P = 0.12); $I^2 = 43\%$		
Total (95% CI)		**-0.11 [-0.54; 0.31]**
Heterogeneity: $Tau^2 = 0.91$; $Chi^2 = 188.42$, df = 26 (P < 0.001); $I^2 = 86\%$		
Test for subgroup differences: $Chi^2 = 47.39$, df = 1 (P < 0.001)		



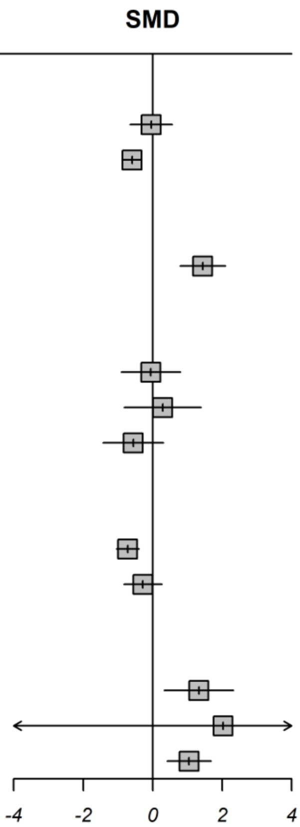
Note: As the studies by Hirvonen 2011 and Tuulari 2013 provided data on brain glucose metabolism during both fasting and hyperinsulinemic clamp, the two studies were excluded among fasting studies to avoid overlapping study population affecting estimates. The standardized mean differences (SMD) changes slightly when the two studies were excluded among the studies performed under hyperinsulinemic clamps, such that SMD was -0.47 SD (95%-CI, -0.73 to -0.22) during fasting and 1.28 SD (95%-CI, 0.81 to 1.76) during hyperinsulinemic clamp.

Supplemental Fig. S4. Funnel plots and Egger's test for identification of publication bias



Supplemental Fig. S5. Forest plot of quantification method used for estimating brain glucose metabolism stratified by metabolic condition (fasting vs insulin stimulation)

Quantification method	Number of studies	Interaction P-value	Hedges' g [95%-CI]
Fasting			
Quantitative	7	0.05	-0.04 [-0.65; 0.56]
Semiquantitative	16		-0.59 [-0.86; -0.33]
Hyperinsulinemic clamp			
Quantitative	6		1.44 [0.79; 2.09]
Fasting - Quantitative			
Type 2 diabetes/Prediabetes	1	0.03	-0.05 [-0.90; 0.80]
Overweight/Obesity	4		0.29 [-0.81; 1.39]
Other insulin resistance-related conditions	2		-0.56 [-1.43; 0.31]
Fasting - Semiquantitative			
Type 2 diabetes/Prediabetes	12	0.05	-0.72 [-1.04; -0.40]
Other insulin resistance-related conditions	4		-0.28 [-0.83; 0.26]
Hyperinsulinemic clamp - Quantitative			
Type 2 diabetes/Prediabetes	3	0.46	1.33 [0.33; 2.32]
Overweight/Obesity	2		2.03 [-7.58; 11.63]
Other insulin resistance-related conditions	1		1.05 [0.42; 1.68]



Note: Summary of standardized mean differences of brain glucose metabolism for quantitative and semi-quantitative studies.

Supplemental Fig. S6. Assessments of influential studies by the leave-one-out method

Fig. S6A All studies (Fasting)

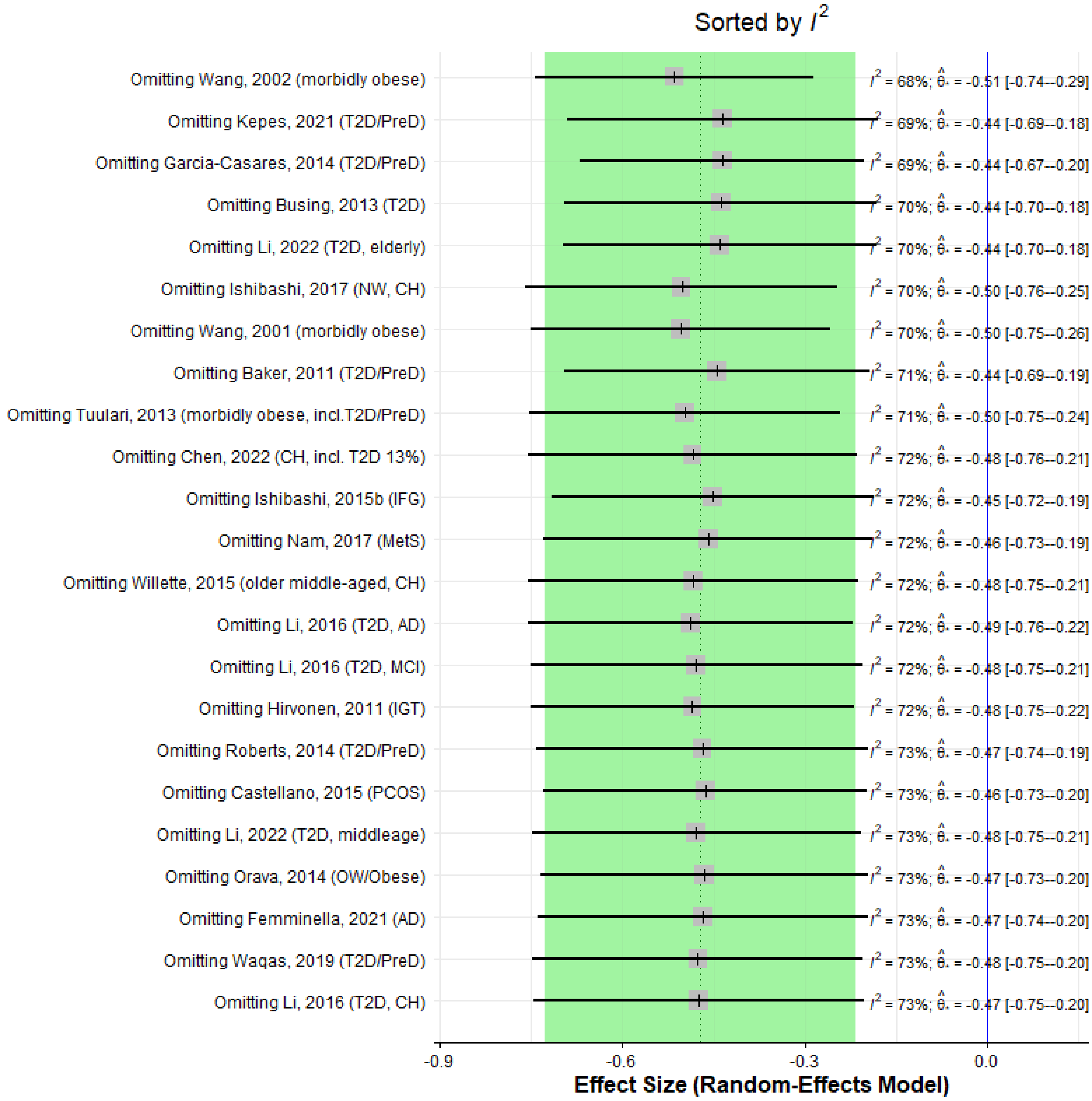


Fig. S6B All studies (insulin stim.)

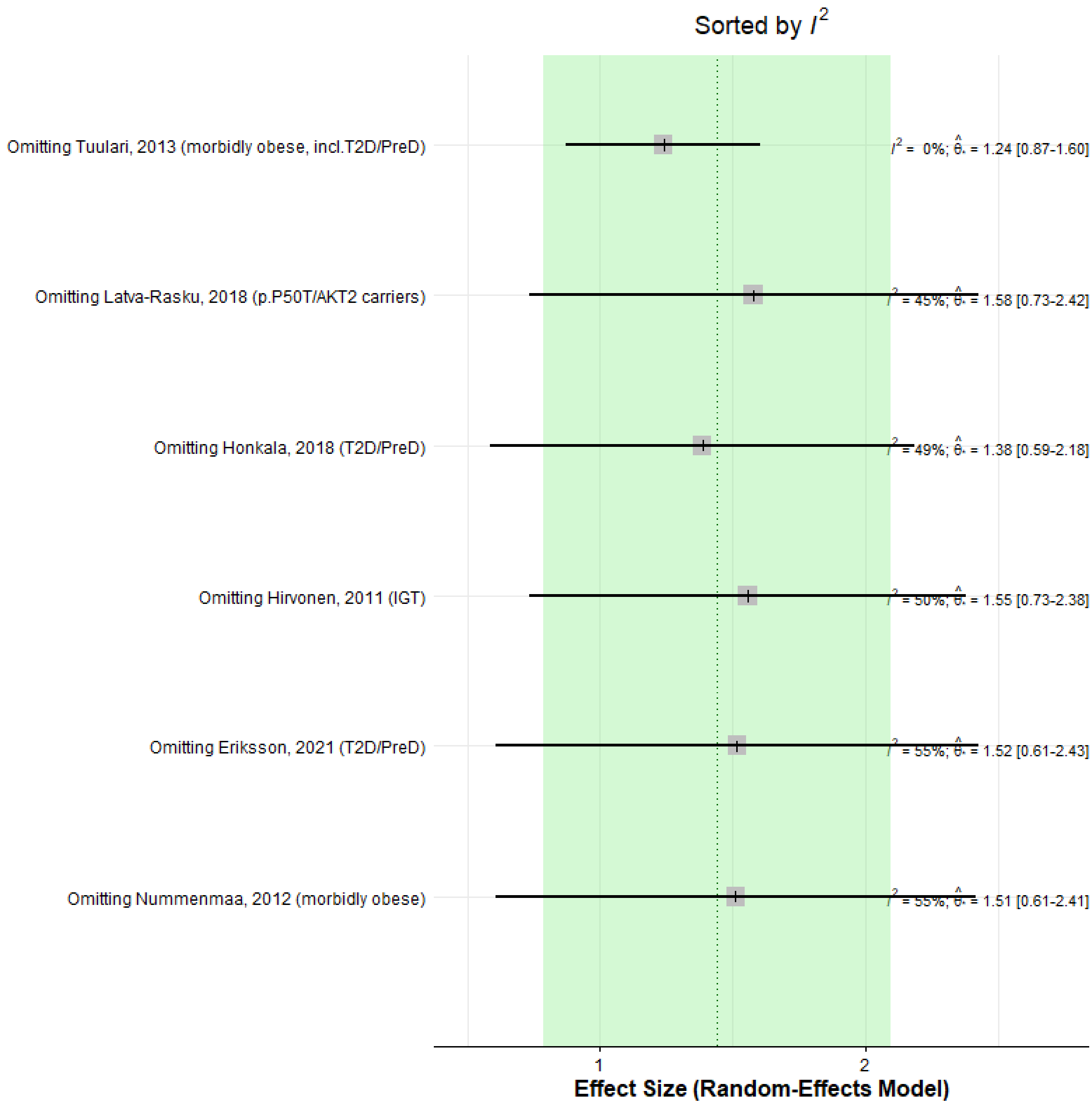


Fig. S6C T2D/PreD (Fasting)

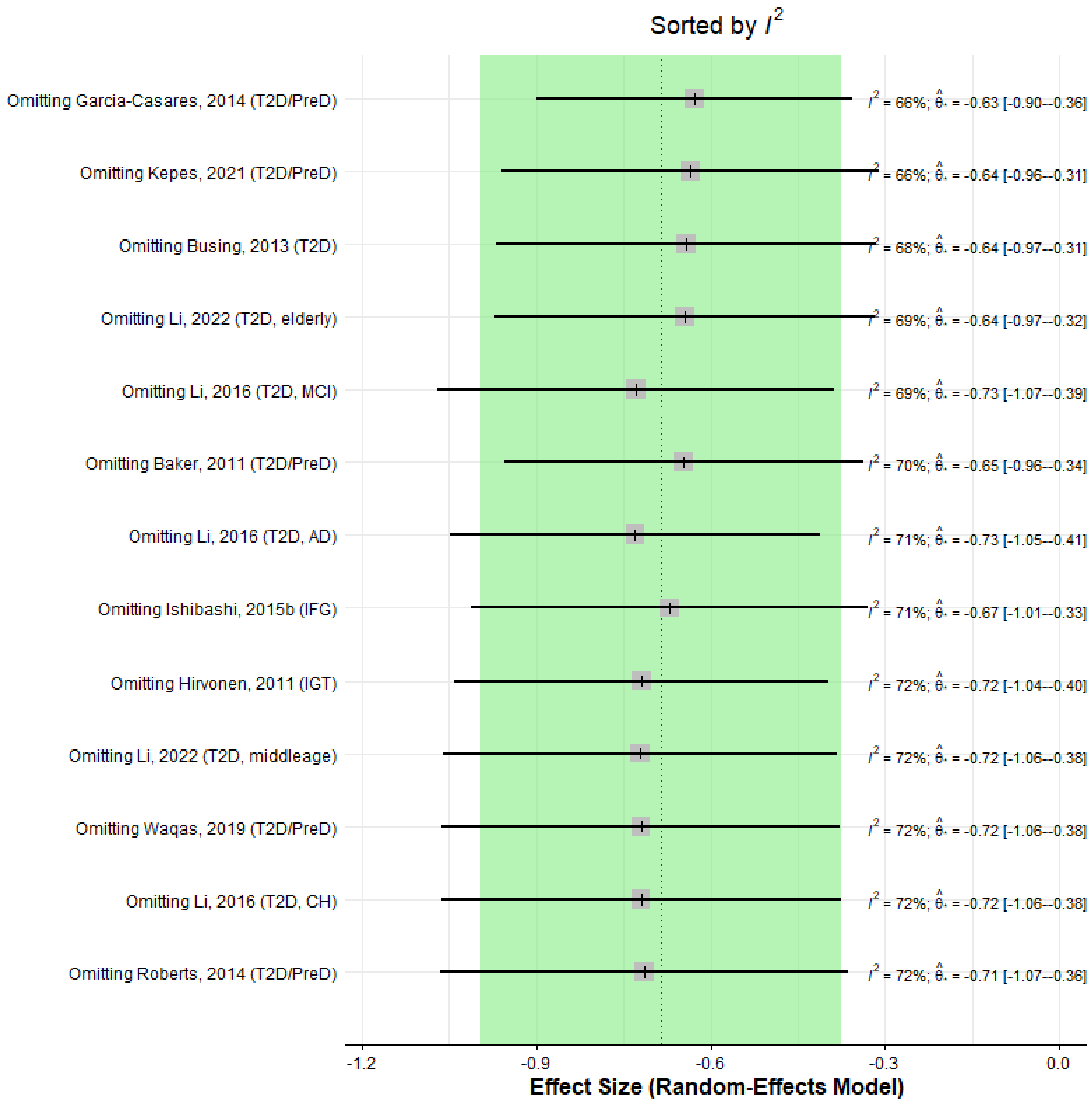


Fig. S6D OW/Obese (Fasting)

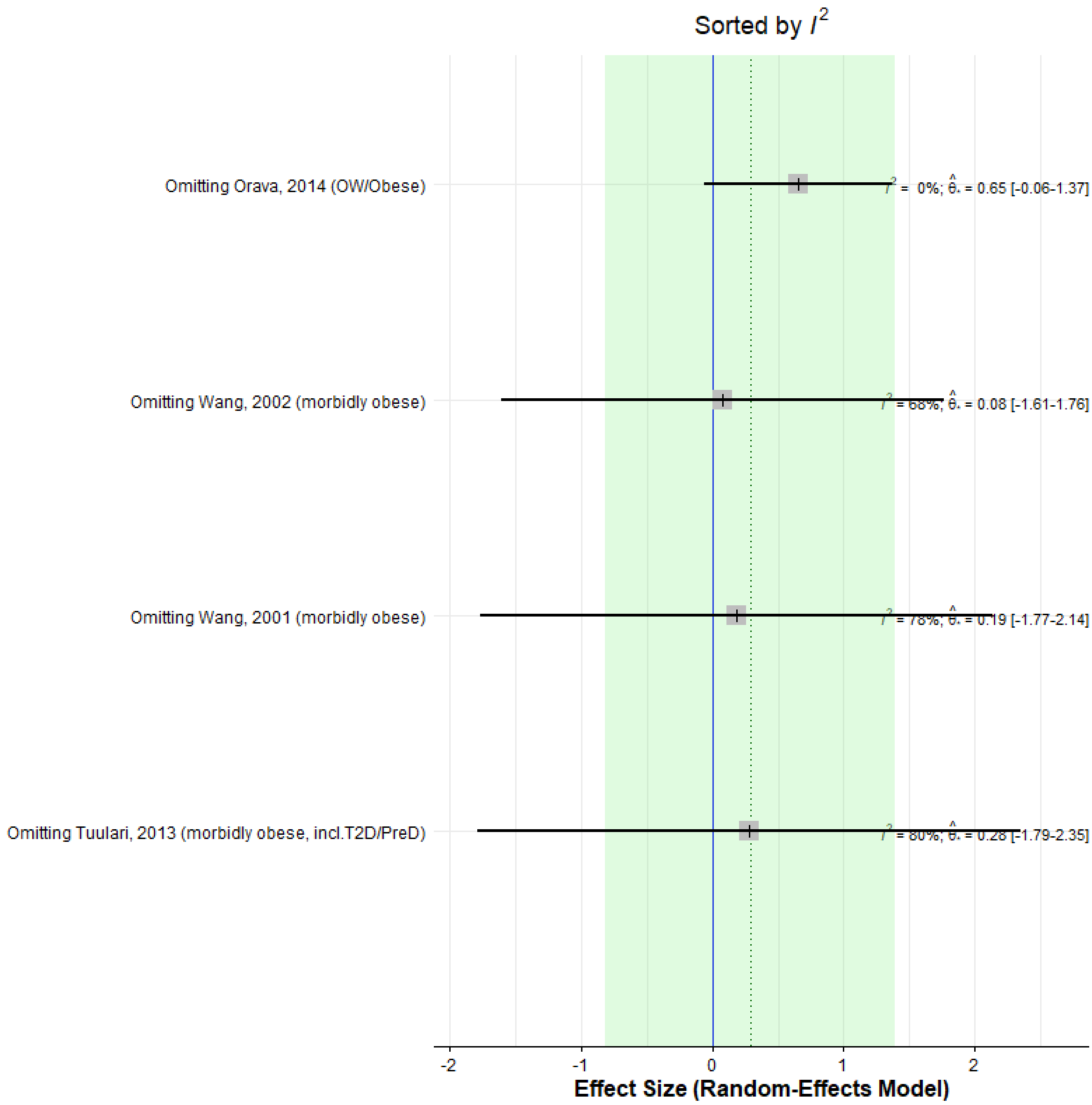


Fig. S6E Other IR-related conditions (Fasting)

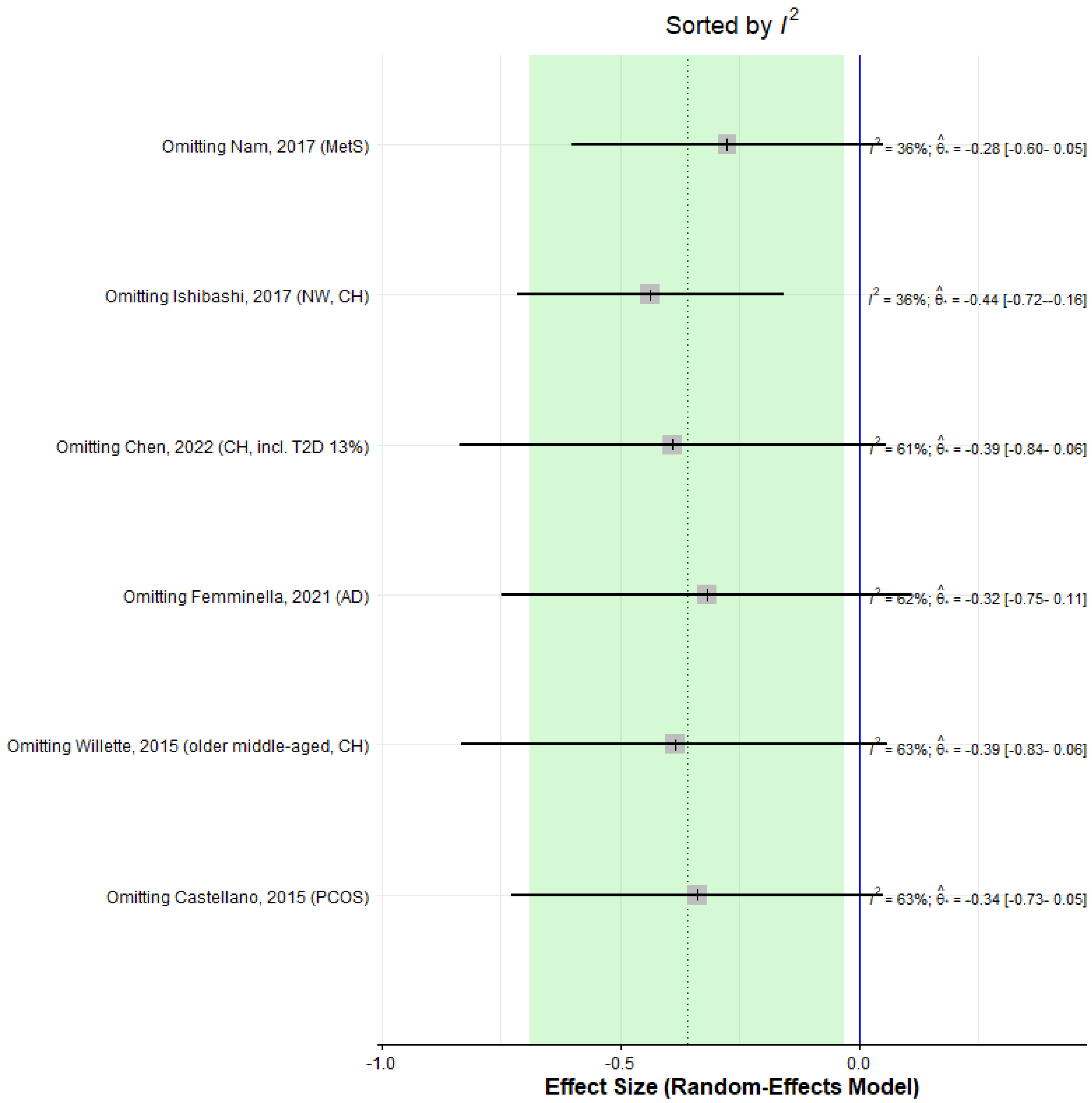
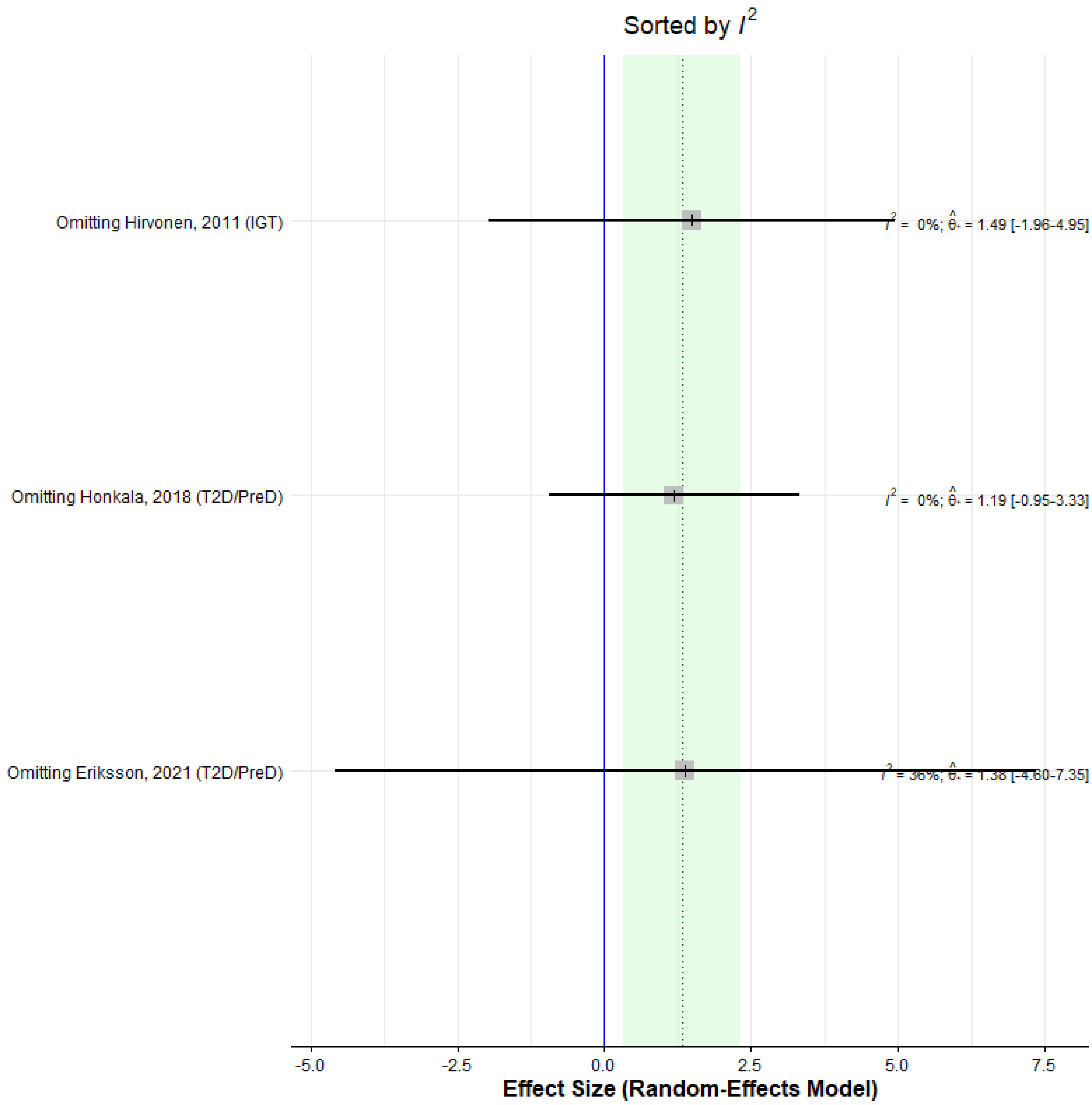


Fig. S6F T2D/PreD (insulin stim.)



Note: Effect sizes when applying the leave-one-out method using the ‘dmetar’ R package (v.0.1.0) to find influential cases.

Supplemental Table S4. References of studies included in the systematic-review and meta-analysis

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7. Honkala SM, Johansson J, Motiani KK, Eskelinen JJ, Virtanen KA, Loyttyniemi E, Knuuti J, Nuutila P, Kalliokoski KK, Hannukainen JC. Short-term interval training alters brain glucose metabolism in subjects with insulin resistance. Journal of Cerebral Blood Flow and Metabolism 2018;38(10):1828-1838
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11. Li YL, Wu JJ, Ma J, Li SS, Xue X, Wei D, Shan CL, Hua XY, Zheng MX, Xu JG. Alteration of Individual Metabolic Network of Brain Based on Jensen-Shannon Divergence Similarity Estimation in the Elderly with Type 2 Diabetes Mellitus. Diabetes 2022;
12. Roberts RO, Knopman DS, Cha RH, Mielke MM, Pankratz VS, Boeve BF, Kantarci K, Geda YE, Jack CR, Jr., Petersen RC, Lowe VJ. Diabetes and elevated hemoglobin A1c levels are associated with brain hypometabolism but not amyloid accumulation. J Nucl Med 2014;55:759-764
13. Waqas K, van Haard PMM, Postema JWA, Schweitzer DH. Diabetes Mellitus-Related Fractional Glucose Uptake in Men and Women Imaged With (18)F-FDG PET-CT. J Endocr Soc 2019;3:773-783
14. Almby KE, Lundqvist MH, Abrahamsson N, Kvernby S, Fahlström M, Pereira MJ, Gingnell M, Karlsson FA, Fanni G, Sundbom M, Wiklund U, Haller S, Lubberink M, Wikström J, Eriksson JW. Effects of Gastric Bypass Surgery on the Brain: Simultaneous Assessment of Glucose Uptake, Blood Flow, Neural Activity, and Cognitive Function During Normo- and Hypoglycemia. Diabetes 2021;70:1265-1277
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