

Protein Hydrolysates and Bioactive Peptides as Mediators of Blood Glucose—A Systematic Review and Meta-Analysis of Acute and Long-Term Studies

Table S1. Database search terms.

Search Category	Search Terms Used
1. Population	(normoglycaemic) OR (normoglycaemia) OR (normoglycemia) OR (healthy) OR (normal) OR (diabetic) OR (diabetes) OR (Prediabetic) OR (prediabetes) OR (T2DM) OR (T2D) OR (NIDDM) OR (adults)
2. Intervention	(hydrolysates) OR (bioactive peptides) OR (peptides) OR (hydrolysed protein) OR (protein extracts)
3. Control	(placebo) OR (protein) OR (intact protein) OR (carbohydrates) OR (CHO) OR (casein) OR (whey) OR (protein isolate) OR (protein concentrate)
4. Outcomes	(glucose) OR (FPG) OR (PPG) OR (glycemic) OR (glycaemia) OR (glycemia) OR (insulin) OR (post-prandial) OR (postprandial) OR (PPGR) OR (OGTT) OR (insulinemic) OR (insulinaemic) OR (HOMA) OR (Homeostatic Model Assessment of Insulin Resistance) OR insulin resistance) OR (IR) OR (glycated hemoglobin) OR (HbA1c) OR (A1C) OR (A1c) OR (glycated haemoglobin) OR (glycosylated haemoglobin)

Table S2. Risk of bias assessment.

Study	Risk of Bias Assessment					
	Domain					Overall
	Randomization Process	Deviation from Intended Intervention	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Results	
Akhavan et al., 2010	some concerns	low risk	low risk	low risk	some concerns	some concerns
Ballard et al., 2009	some concerns	low risk	low risk	low risk	some concerns	some concerns
Ballard et al., 2013	low risk	low risk	some concerns	low risk	low risk	some concerns
Bendtsen et al., 2014	some concerns	low risk	some concerns	low risk	some concerns	some concerns
Calbet et al., 2002	some concerns	low risk	some concerns	low risk	some concerns	some concerns
Chen, 2020	some concerns	low risk	low risk	low risk	some concerns	some concerns
Claessens, 2007	some concerns	Some concerns	some concerns	low risk	some concerns	high risk
Claessens, 2008	some concerns	Some concerns	low risk	low risk	some concerns	some concerns
Claessens, 2009	some concerns	Some concerns	low risk	low risk	low risk	some concerns
Curran, 2019	some concerns	low risk	low risk	low risk	some concerns	some concerns
Dale, 2018	low risk	low risk	low risk	low risk	low risk	low risk
Deglaire, 2009	low risk	low risk	low risk	low risk	some concerns	some concerns
Devasia, 2019	some concerns	low risk	some concerns	low risk	some concerns	high risk
Drummond, 2018	some concerns	low risk	low risk	low risk	some concerns	some concerns
Geerts, 2011	some concerns	low risk	low risk	low risk	some concerns	some concerns
Goudarzi, 2013	some concerns	low risk	some concerns	low risk	some concerns	high risk
Hoefle, 2019	low risk	low risk	low risk	low risk	some concerns	some concerns

Holmer-Jensen, 2012	some concerns	low risk	low risk	low risk	some concerns	some concerns
Horner, 2019	low risk	low risk	low risk	low risk	some concerns	some concerns
Hovaland, 2020	low risk	low risk	low risk	low risk	some concerns	some concerns
Jensen, 2020	some concerns	low risk	low risk	low risk	some concerns	some concerns
Jonker, 2011	some concerns	low risk	low risk	low risk	some concerns	some concerns
King, 2018	some concerns	low risk	some concerns	low risk	some concerns	high risk
Koopman, 2009	some concerns	low risk	some concerns	low risk	some concerns	high risk
Mandres, 2005	some concerns	low risk	Some concerns	low risk	some concerns	high risk
Mandres, 2006	low risk	low risk	low risk	low risk	some concerns	some concerns
Mandres, 2009	some concerns	low risk	low risk	low risk	some concerns	some concerns
Mandres, 2014	some concerns	low risk	low risk	low risk	some concerns	some concerns
Mortensen, 2012	some concerns	low risk	low risk	low risk	some concerns	some concerns
Nakayama, 2018	some concerns	low risk	low risk	low risk	some concerns	some concerns
Plat, 2019	low risk	low risk	low risk	low risk	some concerns	some concerns
Power, 2009	low risk	low risk	low risk	low risk	some concerns	some concerns
Rakvaag, 2019	some concerns	low risk	low risk	low risk	some concerns	some concerns
Sartorius, 2019	low risk	low risk	low risk	low risk	some concerns	some concerns
Van-Loon, 2000	some concerns	low risk	some concerns	low risk	some concerns	high risk
Zhu, 2010	some concerns	low risk	low risk	low risk	some concerns	some concerns

Table S3. GRADE assessment.

Outcome	No. of Trials	No. of Participants	Certainty assessment					Effect Estimate	Grade
			Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations		
PPGR normoglycemia	15	573	Not serious	Not serious	Serious ^b	Not serious	None	-0.22 [-0.40, -0.01]	Moderate
PPGR hyperglycaemia	8	342	Not serious	Not serious	Serious ^b	Not serious	None	-0.88 [-1.37, -0.39]	Moderate
PPIR normoglycaemia	12	470	Not serious	Serious ^a	Serious ^b	Not serious	None	12.98 [2.73, 23.23]	Low
PPIR hyperglycaemia	7	322	Not serious	Serious ^a	Serious ^b	Not serious	None	23.05 [7.53, 38.57]	Low
FBG	6	266	Not serious	Serious ^a	Serious ^b	Serious ^c	None	-0.83 [-1.50, -0.16]	Very Low
HbA_{1c}	3	161	Not serious	Serious ^a	Serious ^b	Very serious ^e	None	-7.99 [-11.04, -4.95]	Very Low
HOMA-IR	6	306	Not serious	Serious ^a	Serious ^b	Very serious ^{c,d}	None	-0.71 [-1.58, 0.17]	Very low

PPGR, Postprandial Glucose Response; PPIR, Postprandial Insulin Response; FBG, Fasting Blood Glucose; HbA_{1c}, Glycated haemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; a. Due to unexplained variability among the studies; b. Due to variations in the control groups; c. Different arms with same publications or different studies with same authors. d. The 95% confidence interval encompassed both positive effects and adverse effects. e. Due to small number of studies.

a. High heterogeneity between studies that was not improved through further subgroup analyses, meta-regression, or sensitivity analyses.

b. There was no standardized control for all studies. Control varied between carbohydrates, reference popular proteins such as Casein or Whey, isolate protein (unhydrolysed), milk and mixture of protein and amino acids. In addition, the form of the control was different in some studies; some were given as drinks others as tables.

c. Publications bias may occur when including different studies/arms with same authors as authors may consistently report similar findings across multiple studies, there may be a risk of confirmation bias. This occurs when researchers selectively publish or emphasize studies that confirm their hypotheses while neglecting those that do not.

d. No significant change. The change was in the same direction with the intervention, however the 95% confident intervals crossed one (-1.58 to 0.17).

e. only 3 studies were included in the analysis. With a small number of studies, it may be challenging to assess and explain heterogeneity. Even minor differences between studies can disproportionately influence the overall results, and there may not be enough statistical power to detect and understand sources of heterogeneity.

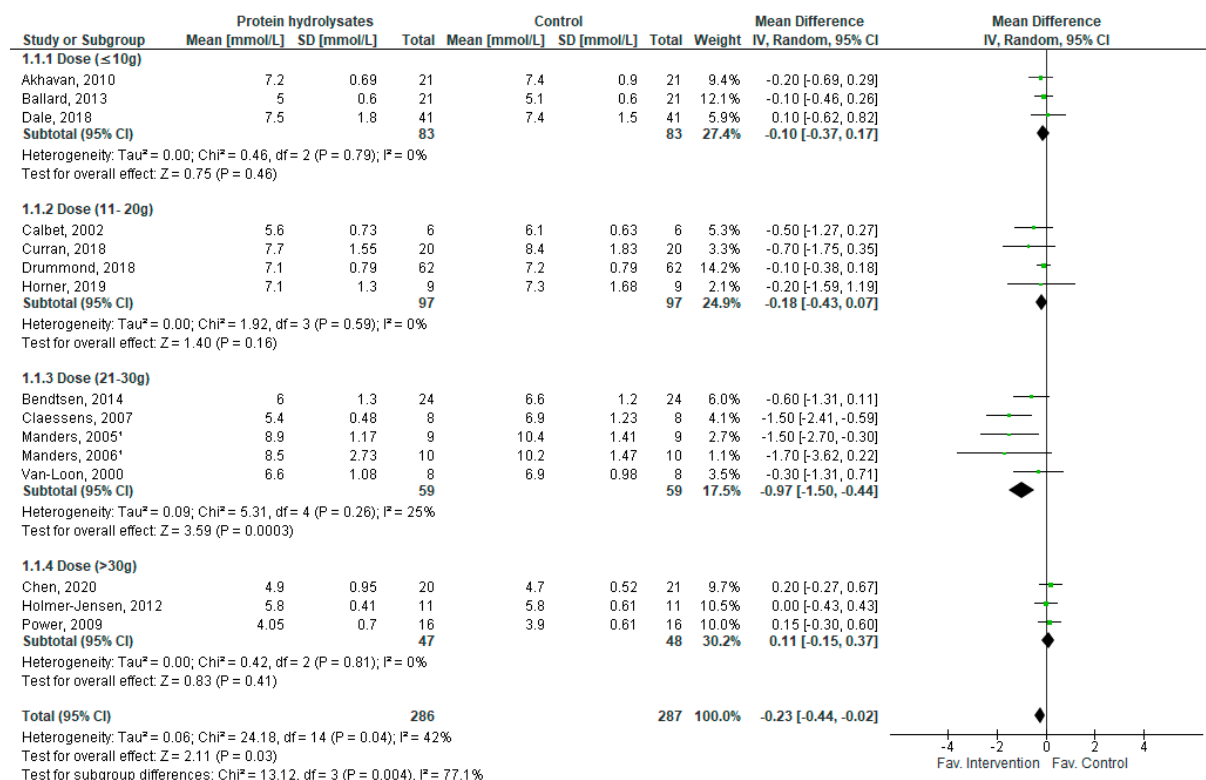


Figure S1. Subgroup analysis of acute studies investigating the effect of different doses of protein hydrolysate consumption on postprandial glucose response in adults with normoglycaemia.

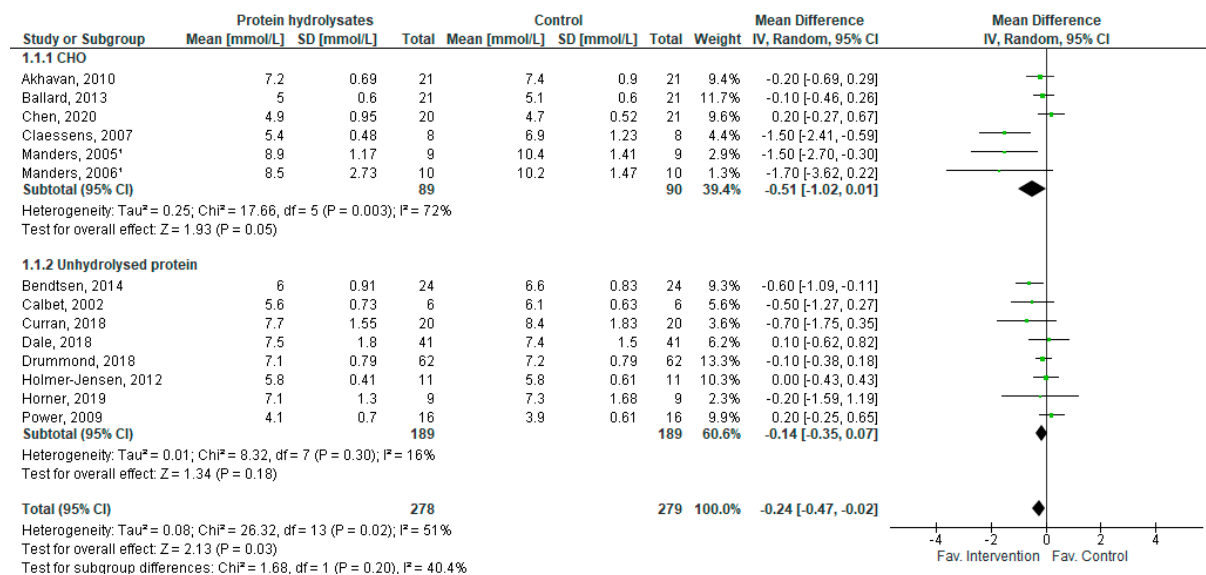


Figure S2. Subgroup analysis by control type on acute studies investigating acute glucose response after protein hydrolysates consumption in adults with normoglycaemia.

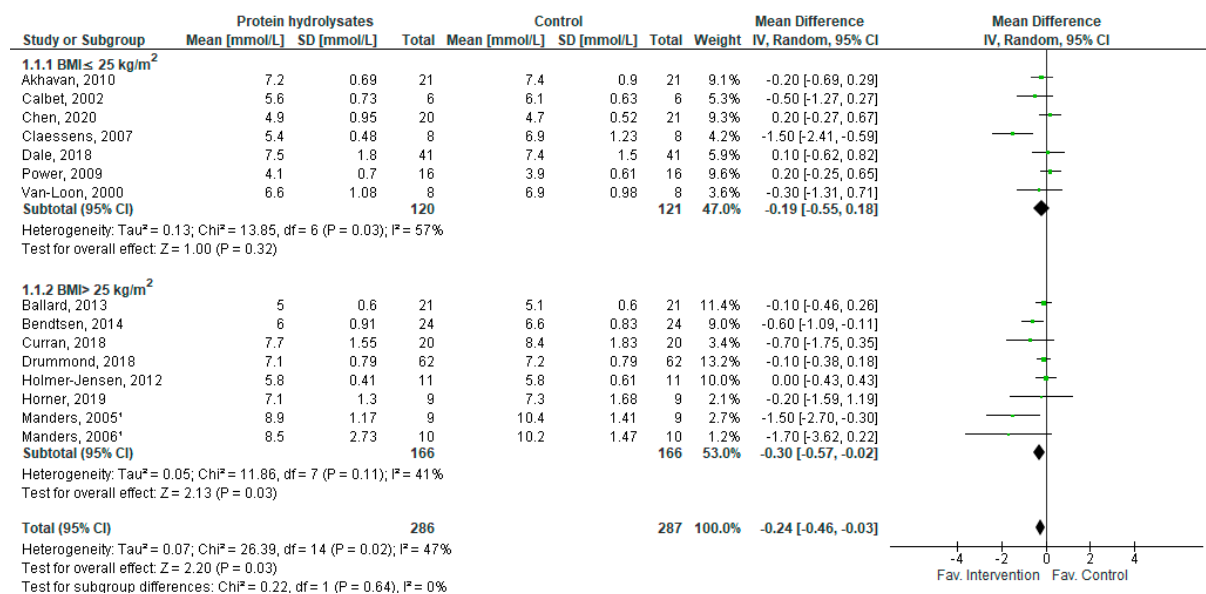


Figure S3. Subgroup analysis by BMI on acute studies investigating postprandial glucose response after protein hydrolysates consumption in normoglycaemic adults.

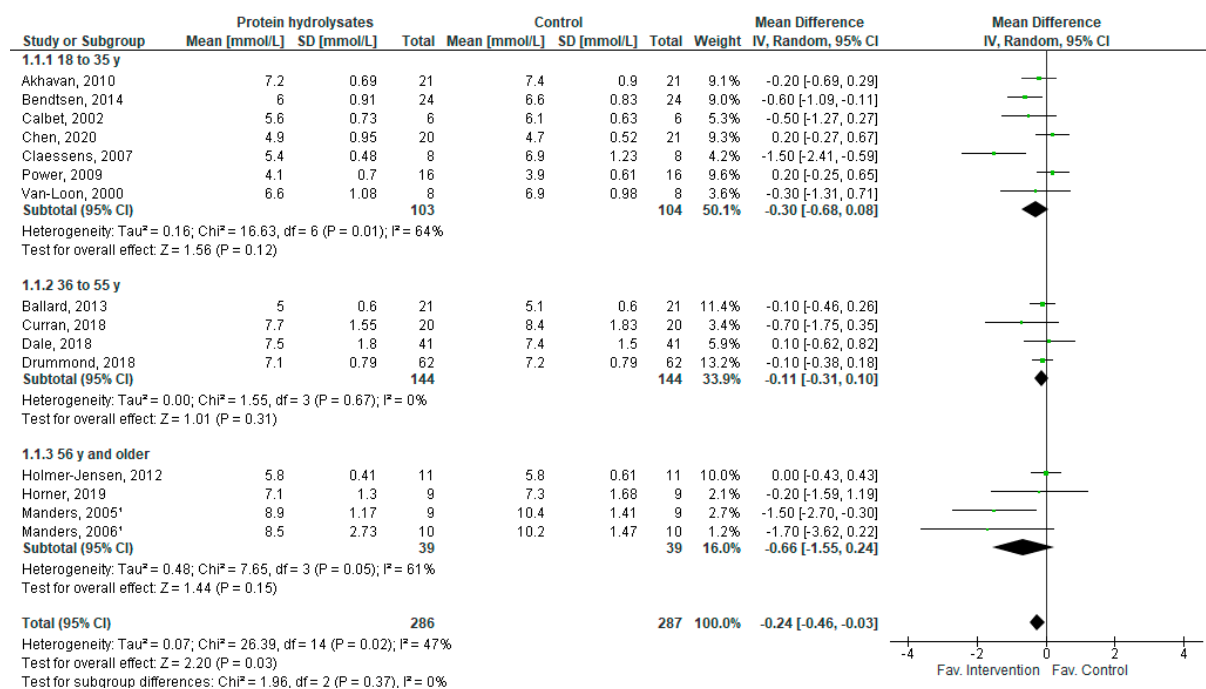


Figure S4. Subgroup analysis of acute studies investigating the impact of the participants' age on the postprandial glucose in response to protein hydrolysates consumption in adults with normoglycaemia.

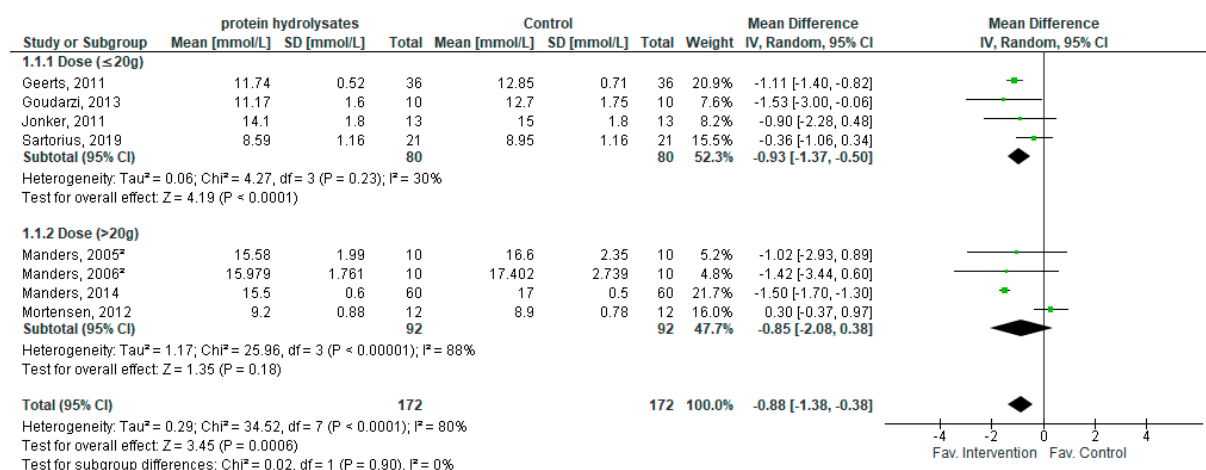


Figure S5. Subgroup analysis of acute studies investigating the effect of different doses of protein hydrolysates consumption on postprandial glucose response in adults with hyperglycaemia.

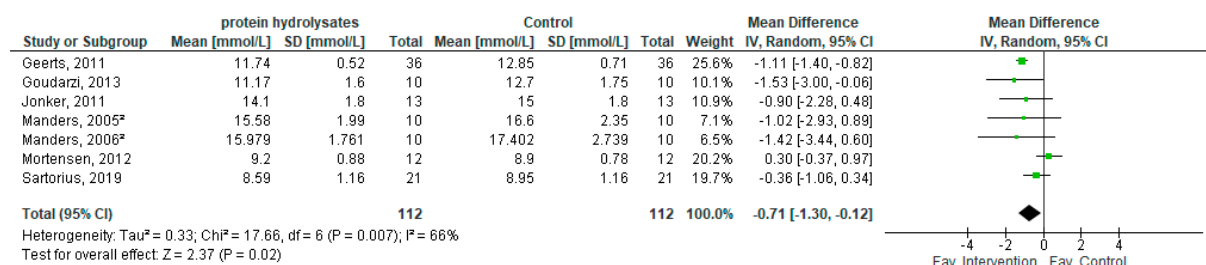


Figure S6. Sensitivity analysis by removing one study based on BMI of the studies investigating postprandial glucose response after protein hydrolysates consumption in adults with hyperglycaemia (Only studies BMI <30 Kg/m 2 were included in this analysis).

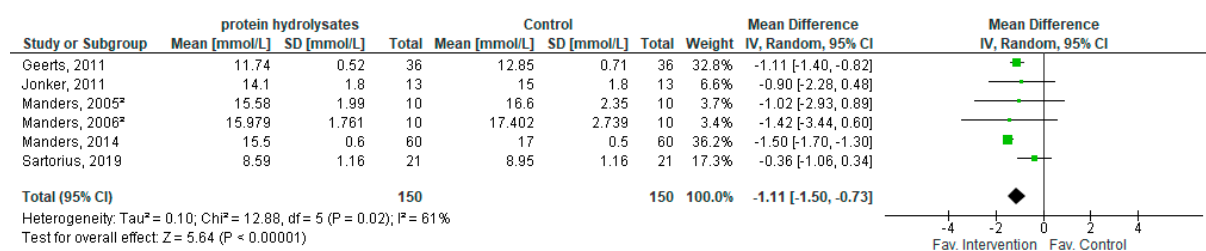


Figure S7. Sensitivity analysis by removing two studies based on control type of the studies investigating glucose response after protein hydrolysates consumption in adults with hyperglycaemia (Only studies with CHO control were included in this analysis).

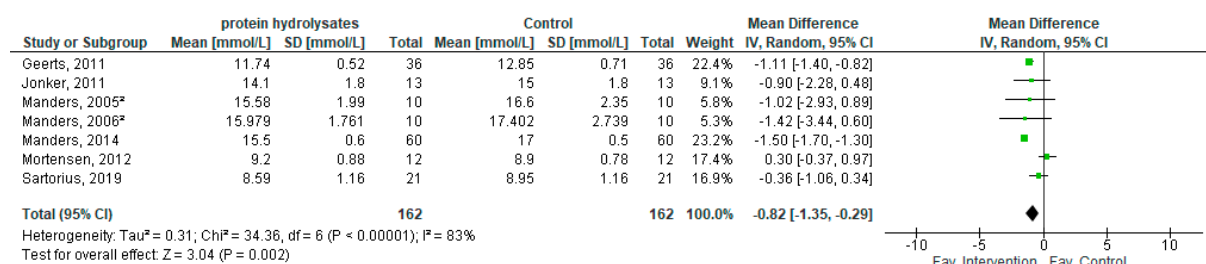


Figure S8. Sensitivity analysis by removing one study based on participants' age of the studies investigating postprandial glucose response after protein hydrolysates consumption in adults with hyperglycaemia (Only studies with older adulthood (> 55 years) were included in this analysis).

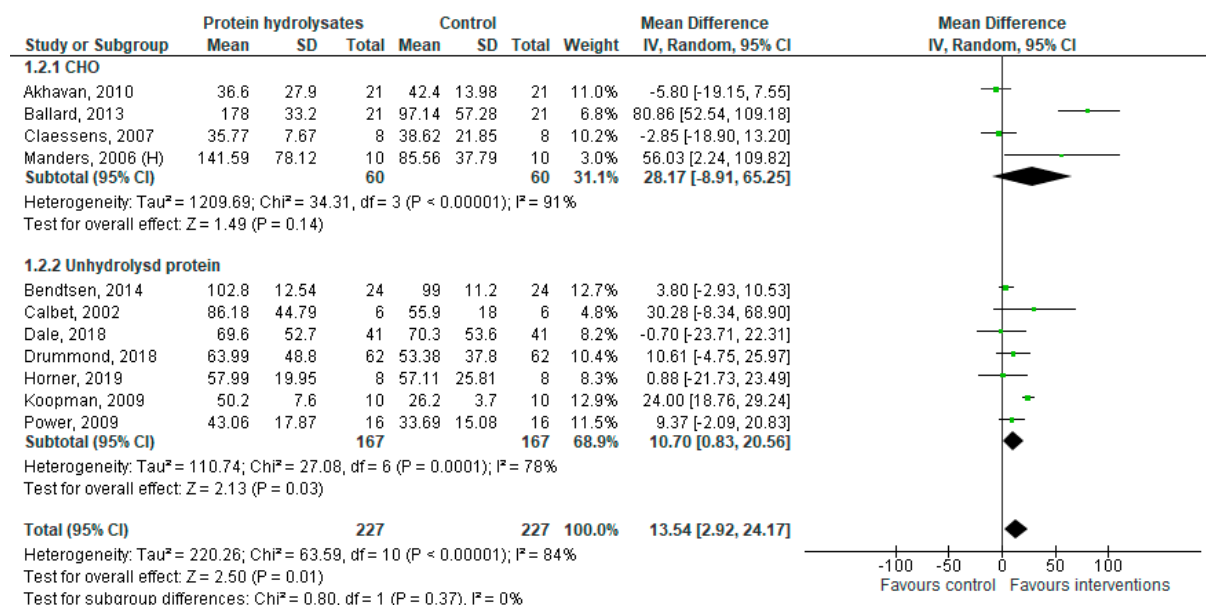


Figure S9. Subgroup analysis by control type on acute studies investigating postprandial insulin response after protein hydrolysates consumption in normoglycaemic adults

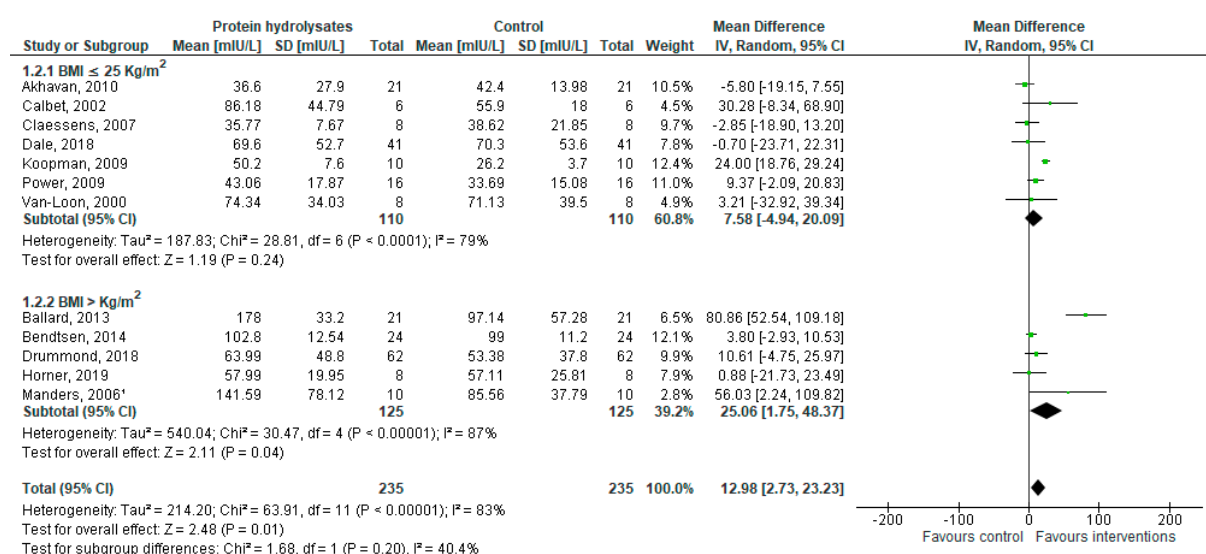


Figure S10. Subgroup analysis by BMI on acute studies investigating postprandial insulin response after protein hydrolysates consumption in adults with normoglycaemia.

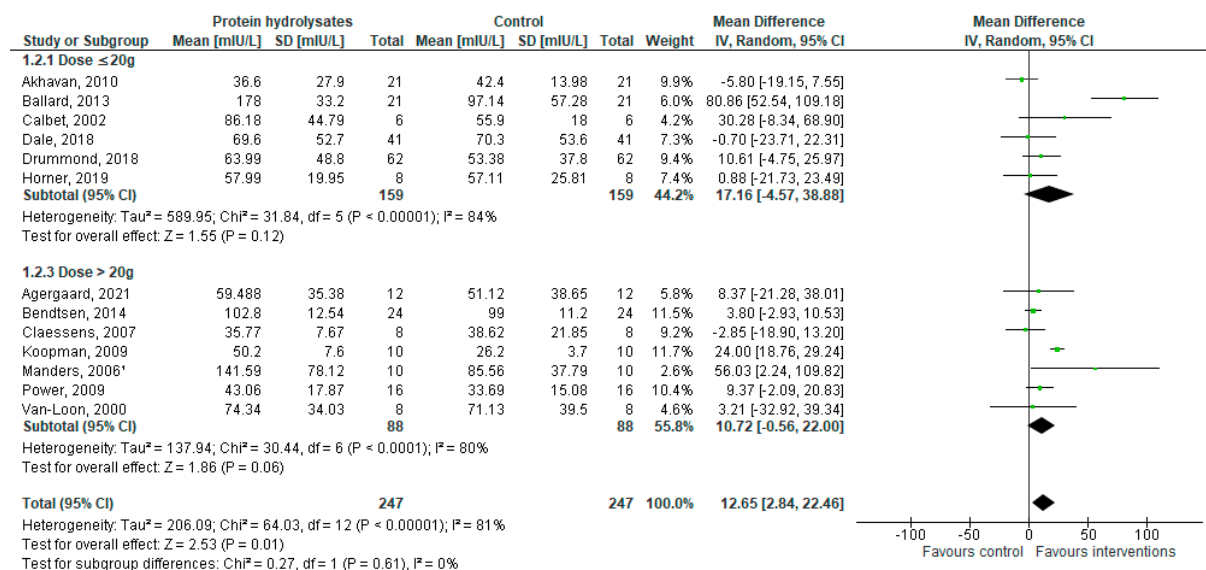


Figure S11. Subgroup analysis of acute studies investigating the effect of different doses of protein hydrolysates consumption on postprandial insulin response in adults with normoglycaemia.

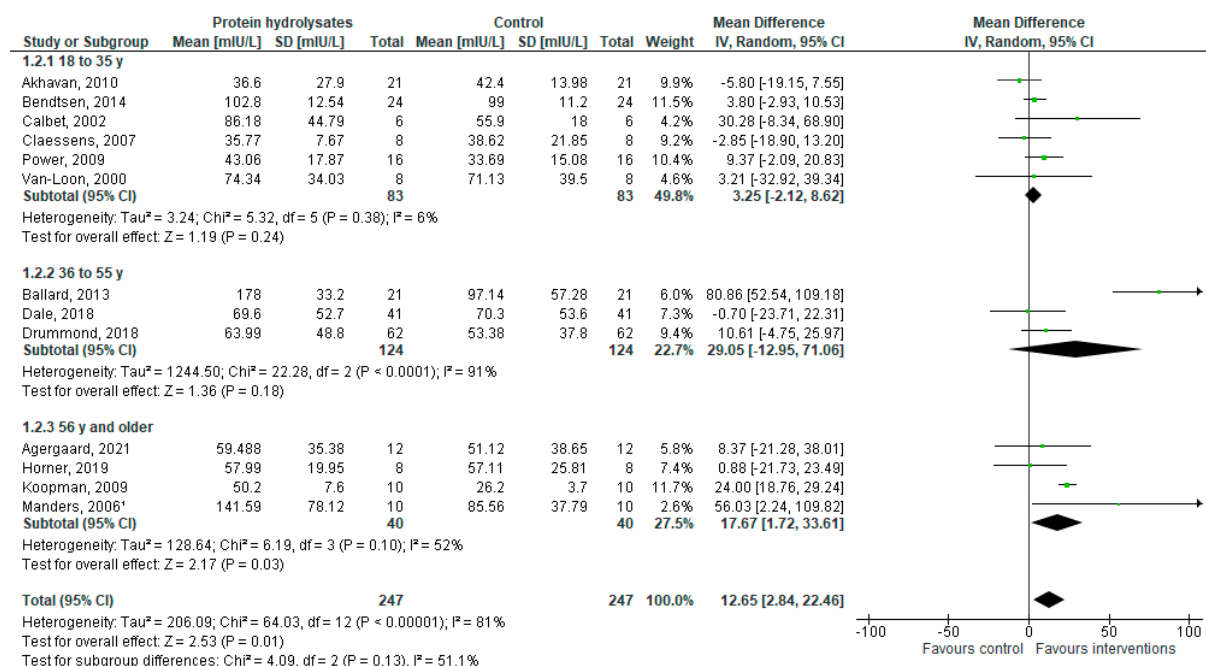


Figure S12. Subgroup analysis of acute studies investigating the impact of the participants' age on the postprandial insulin in response to protein hydrolysates consumption in adults with normoglycaemia.

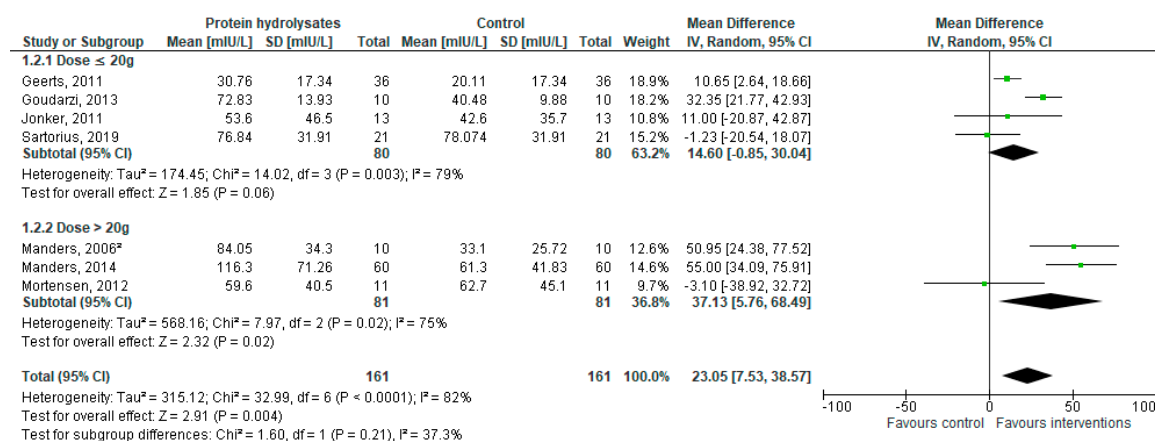


Figure S13. Subgroup analysis of acute studies investigating the effect of different doses of protein hydrolysates consumption on postprandial insulin response in adults with hyperglycaemia.

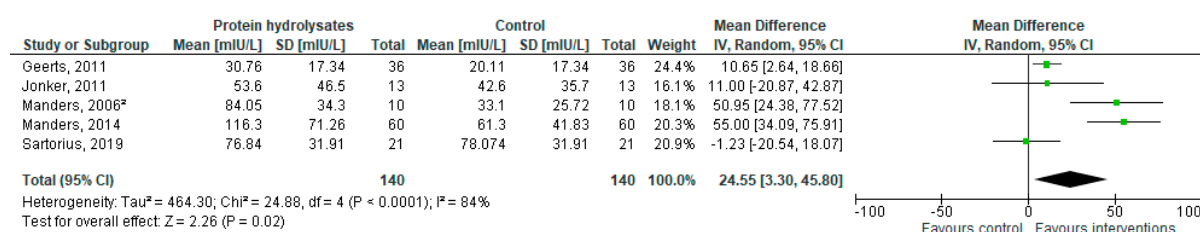


Figure S14. Sensitivity analysis by removing two studies based on control type of the studies investigating postprandial insulin response after protein hydrolysates consumption in adults with hyperglycaemia (Only studies with CHO control were included in this analysis).

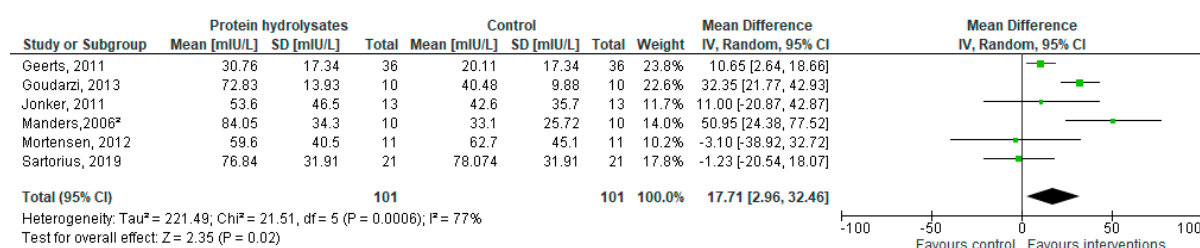


Figure S15. Sensitivity analysis by removing one study based on BMI of the studies investigating postprandial insulin response after protein hydrolysates consumption in adults with hyperglycaemia (Only studies BMI < 30 Kg/m² were included in this analysis).

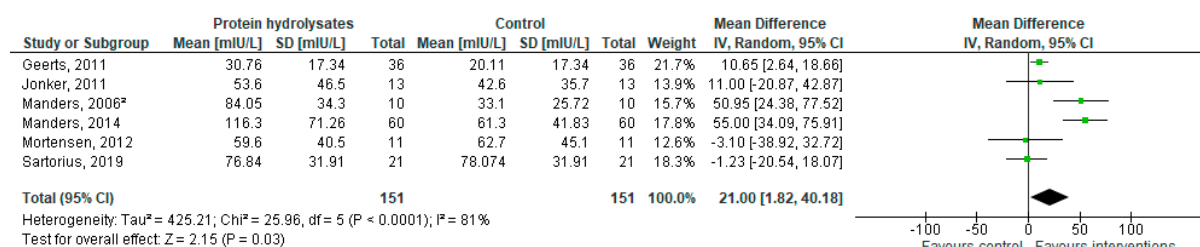


Figure S16. Sensitivity analysis by removing one study based on participants' age of the studies investigating postprandial insulin response after protein hydrolysates consumption in adults with hyperglycaemia (Only studies with older adulthood (>55 years) were included in this analysis).

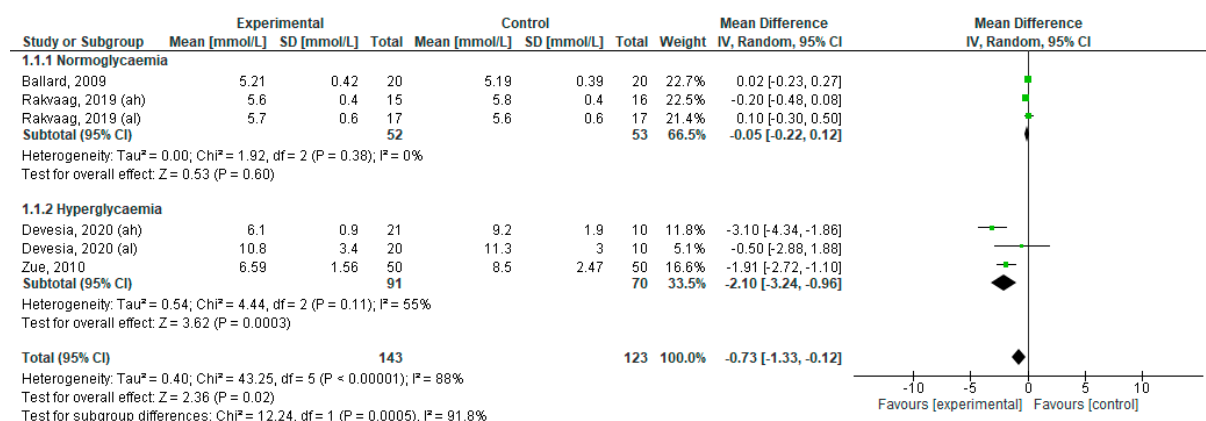


Figure S17. Subgroup analysis of long-term studies investigating the impact of the glycaemic status of the participants on fasting glucose levels in response to protein hydrolysates consumption.