Supplementary Materials

The search terms of casein hydrolysate were used to search:

("casein hydrolysate" [Supplementary Concept]) AND ("blood pressure"[Mesh])

("casein hydrolysate" [Supplementary Concept]) AND ("cholesterol" [Mesh])

("casein hydrolysate" [Supplementary Concept]) AND ("triglycerides" [Mesh])

("casein hydrolysate" [Supplementary Concept]) AND ("blood glucose" [Mesh])

(ALL=(casein hydrolysate)) AND ALL=(blood pressure)

(ALL=(casein hydrolysate)) AND ALL=(cholesterol)

(ALL=(casein hydrolysate)) AND ALL=(triglycerides)

(ALL=(casein hydrolysate)) AND ALL=(blood glucose)

The references of included RCTs in this article:

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Table S1. Characteristics of the publications included in the meta-analysis.

Article	Study design	Source of hydroly-sate	Preparation method	Intervention diet	Control diet	Extracted out-come(s)	Duration	Health status	Population size n (Ctrl, Inter)	Location	Mean age, y
Akazawa N, 2018	R, DB	Milk	Fermentation	LTPs	Control	SBP,DBP,TG,TC,FBG	8 W	1	15 (8,7)	Japan	52-75
Cadée, 2007	R, DB	Casein	-	C12 peptide	Control	SBP,DBP	4 W	3	48 (24,24)	China	>50
Cicero A. F. G, 2012	R, DB	Casein	-	LTPs	Control	SBP,DBP	4 W	2,4	164 (82,82)	Italy	43.85±11.11
Cicero A. F. G, 2010	R, SB, C	Casein	Enzyme	LTPs	Control	SBP,DBP	4 W	1,2	55 (55,55)	Italy	40.3±9.8
Cicero A. F. G, 2016	R, DB, C	Casein	Enzyme	LTPs	Control	SBP,DBP	4 W	7	40 (40,40)	Italy	40-75
Engberink M. F, 2008	R, DB	Casein	Fermentation	LTPs	Control	SBP,DBP	8 W	2,6	67 (32,35)	Dutch	58.8±9.1
Engberink M. F, 2008	R, DB	Casein	Enzyme	LTPs	Control	SBP,DBP	8 W	2,6	64 (32,32)	Dutch	54.2±8.8
Engberink M. F, 2008	R, DB	Casein	Synthesis	LTPs	Control	SBP,DBP	8 W	2,6	68 (32,36)	Dutch	59.5±8.2
Germino F W, 2010	R, DB	-	-	LTPs	Control	SBP	6 W	4,5	81 (29,52)	America	32–78
Hirota T, 2007	R, DB, C	Casein	Enzyme	LTPs	Control	SBP,DBP,TG,TC, FBG	1 W	4	24 (24,24)	Japan	54.1±8.1
Igase M, 2021	R, DB	Casein	-	LTPs	Control	SBP,DBP,TG,LDL,HDL	48 W	1	80 (44,36)	Japan	71.7±9.2
Ishida Y, 2011	R, DB	Casein	Enzyme	LTPs	Control	SBP,DBP,TG,TC, FBG	4 W	1,2,4	48 (24,24)	Japan	49.3±11.9
Jauhiainen T, 2012	R, DB	-	-	Peptide	Control	SBP,DBP	3 M	4	89 (44,45)	Finland	49±5
Mizuno S, 2005	R, SB	Casein	Enzyme	IPP, VPP	Control	SBP,DBP,TG,TC,HDL, FBG	6 W	4	41 (20, 21)	Japan	46±14.7
Mizuno S, 2005	R, SB	Casein	Enzyme	IPP, VPP	Control	SBP,DBP,TG,TC,HDL, FBG	6 W	2	24 (12, 12)	Japan	42.6±12.1
Nakamura T, 2011	R, DB	-	-	LTPs	Control	SBP,DBP,TG,TC,LDL,HDL, FBG	8 W	6	90 (45,45)	Japan	50-69

Sano J, 2005	R, DB	Casein	Enzyme	LTPs	Control	SBP,DBP,TC,HDL, FBG	12 W	2,4	144 (72,72)	Japan	51±10
Usinger L, 2010	R, DB	-	Fermentation	LTPs	Control	TG,TC,LDL,HDL	8 W	3,6	48 (15,32)	Denmark	54±11
Van D, 2008	R, DB	Casein	Enzyme	ELTP	Control	SBP,DBP	8 W	4	271(137,134)	Dutch	60±7
Yamasue K, 2010	R, DB, C	-	Fermentation	LTPs	Control	SBP,DBP	8 W	2	22 (22,22)	Japan	63.3±4.6
Yoshizawa M, 2010	R	-	Fermentation	LTPs	Control	SBP,DBP,TG,TC,LDL,HDL	8 W	1	22 (10,12)	Japan	58±1
Yoshizawa M, 2009	R	Casein	Fermentation	LTPs	Control	SBP,DBP,TG,TC,LDL,HDL	8 W	1	28 (13,15)	Japan	59±1
Kajimoto O, 2002	R, DB	Milk	Fermentation	LTPs	Control	SBP,DBP,TG,TC, HDL	8 W	4	64 (33,31)	Japan	50±11
Hata Y, 1996	R	Milk	Fermentation	Sour milk	Control	SBP,DBP,TG,TC,HDL, FBG	8 W	6	30 (13,17)	Japan	40-86
Jauhiainen T, 2005	R, DB	Milk	Fermentation	Sour milk	Control	SBP,DBP,TG,LDL	10 W	6	94 (47,47)	Finland	55±11
Jauhiainen T, 2010	R, DB	Milk	Fermentation	Peptide	Control	SBP,DBP	24 W	6	89 (45,44)	Finland	49±5
Mizushima S, 2004	R, DB	Milk	Fermentation	Sour milk	Control	SBP,DBP,TG,TC,HDL	4 W	6	46 (23,23)	Japan	48.5±8.9
Seppo L, 2002	R, DB	Milk	Fermentation	LTPs	Control	SBP,DBP	21 W	6	36 (17,19)	Finland	47.9±6.9
Lu T M，2018	R, DB	Milk	Fermentation	LTPs	Control	TG,TC,LDL,HDL	8 W	3	45 (23,22)	China	30-65

Data are presented as mean ± sd or as a range.
Study design: R, randomized; DB, double-blinded; SB, single-blinded; C, crossover design.
Intervention diet: LTPs, lactotripeptides; IPP, Isoleucine-Proline-Proline; VPP, Valine-Proline-Proline.
Extracted outcome(s): SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein-cholesterol; FBG, fasting blood pressure.
Duration: W, week; M, month.
Health status: 1, health; 2, high-normal blood pressure; 3, prehypertension; 4, Stage I hypertension (mild hypertension); 5, Stage II hypertension (moderate hypertension); 6, hypertension; 7, metabolic syndrome.
Population size: Ctrl, control group; Inter, intervention group.
-, not reported.

Table S2. P value of Egger's test analyses on SBP, DBP, TC, LDL, HDL, TG, and FBG from included RCTs articles.

	$P_{\text{Egger's test}}$
SBP	0.01
DBP	0.03
TC	0.304
LDL	0.483
HDL	0.396
TG	0.473
FBG	0.430

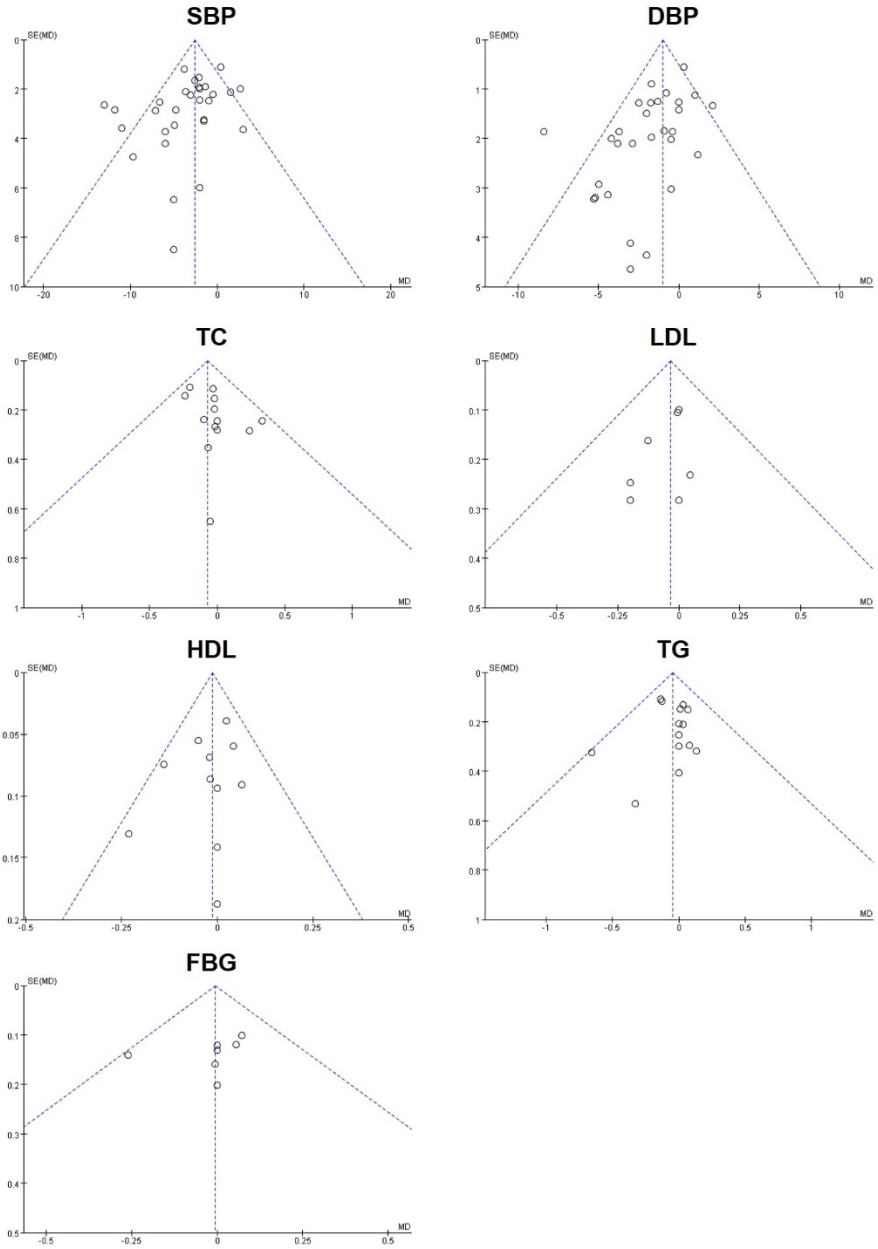


Figure S1. Funnel plots on SBP, DBP, TC, LDL, HDL, TG, FBG in the overall effect analysis.

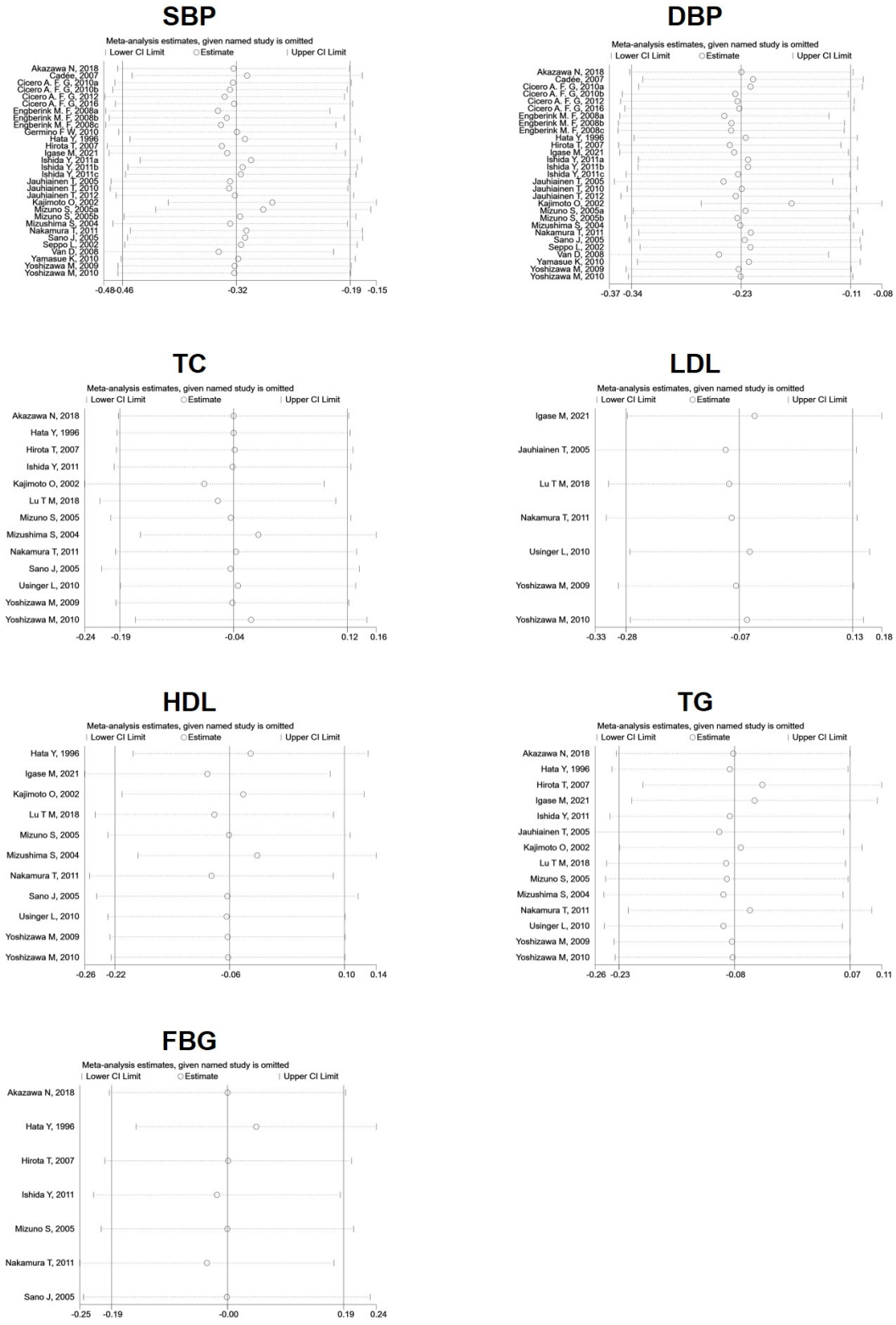


Figure S2. Sensitivity analysis on SBP, DBP, TC, LDL, HDL, TG, FBG in the overall effect analysis.

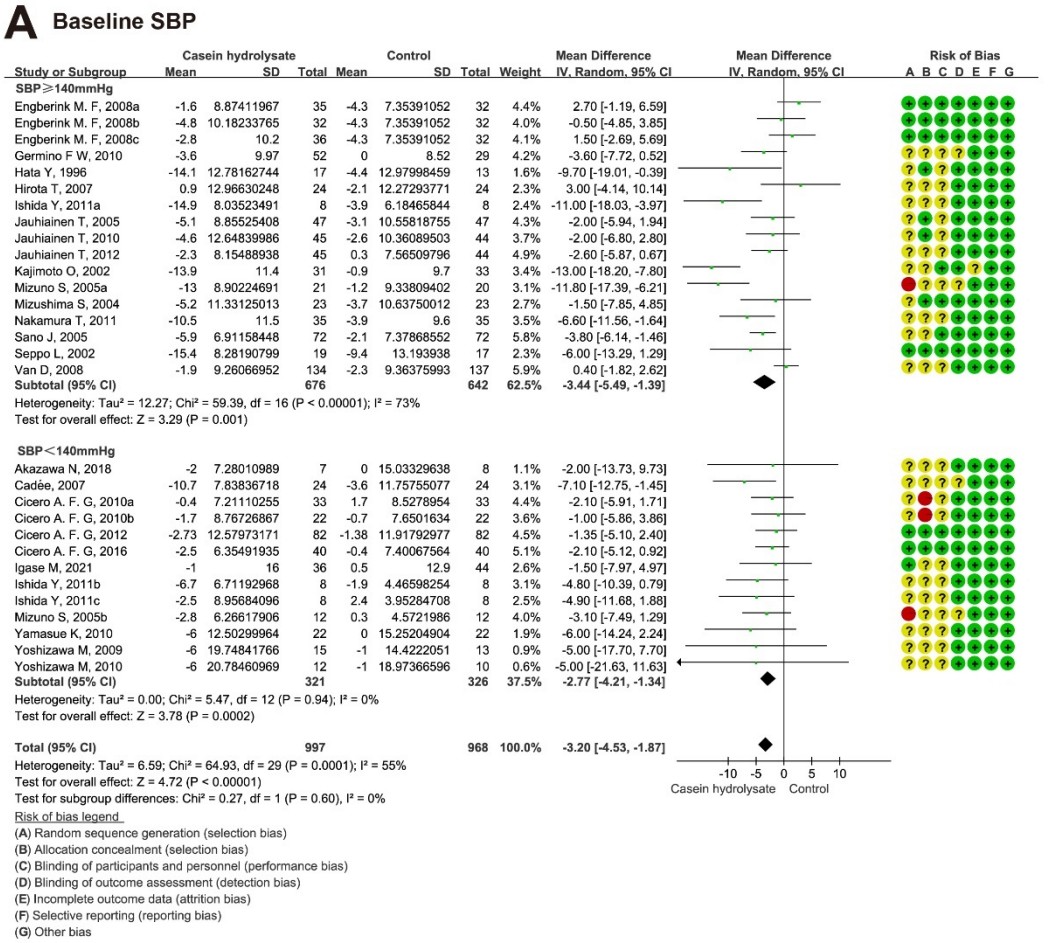
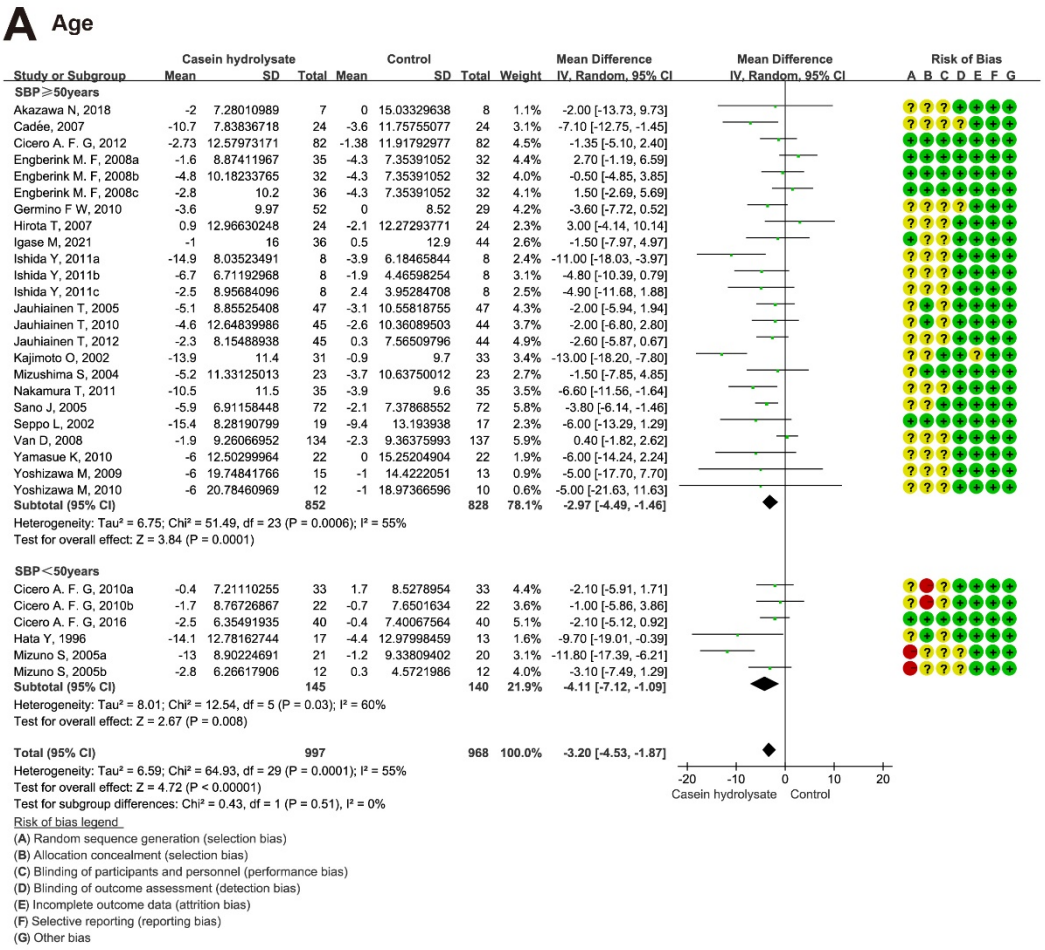


Figure S3. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on SBP (mmHg) in baseline SBP analysis. The results represented the changes of SBP in baseline SBP subgroup with the casein hydrolysate intervention in comparison with the control diet.



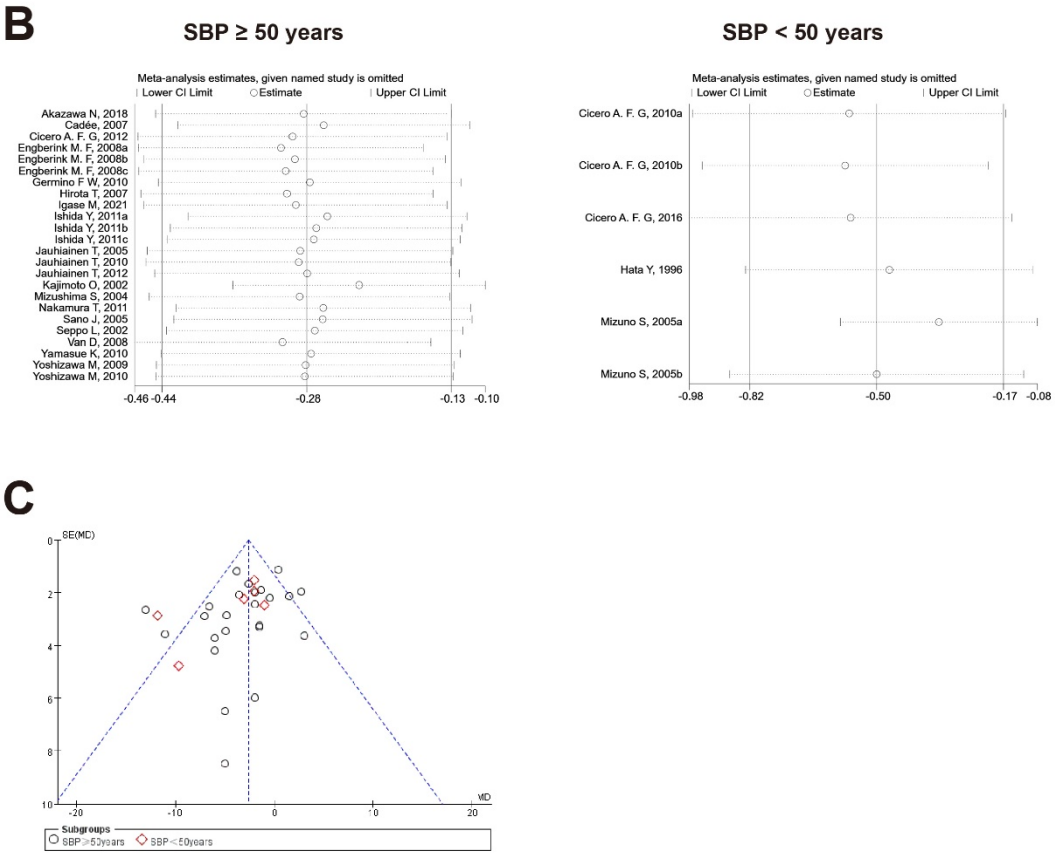
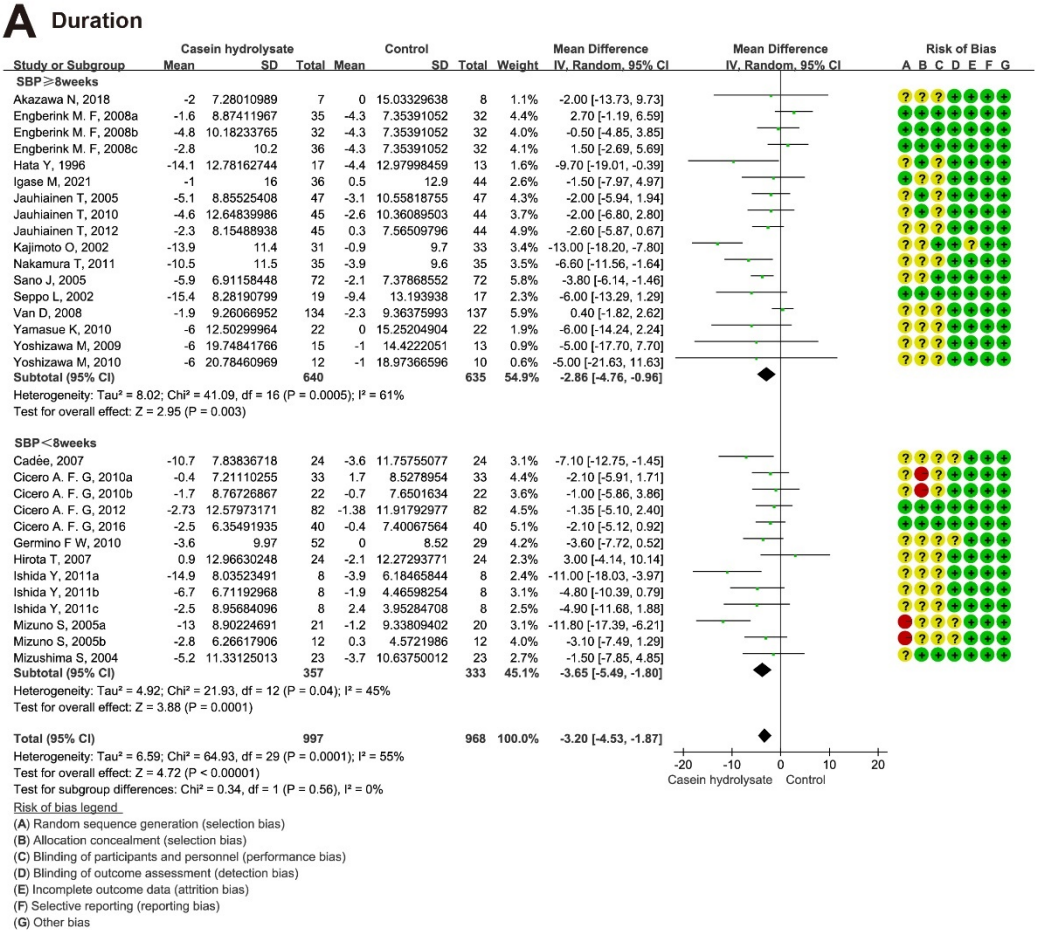
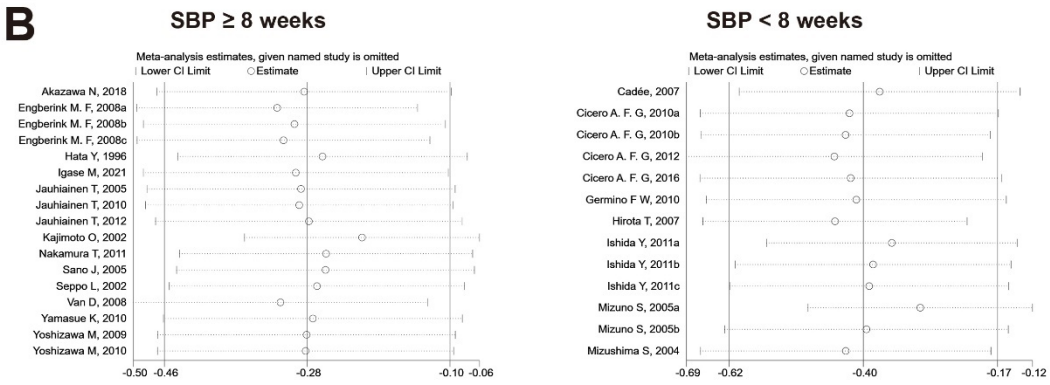


Figure S4. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on SBP (mmHg) in the age analysis. The results represented the changes of SBP in the age subgroup with the casein hydrolysate intervention in comparison with the control diet.





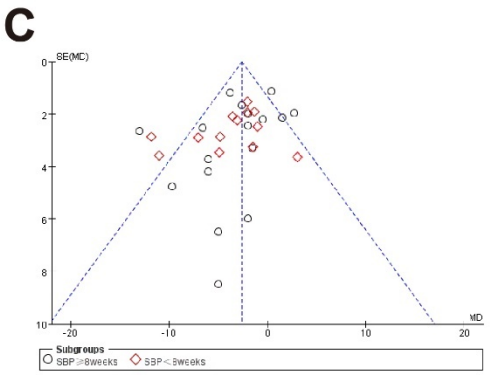
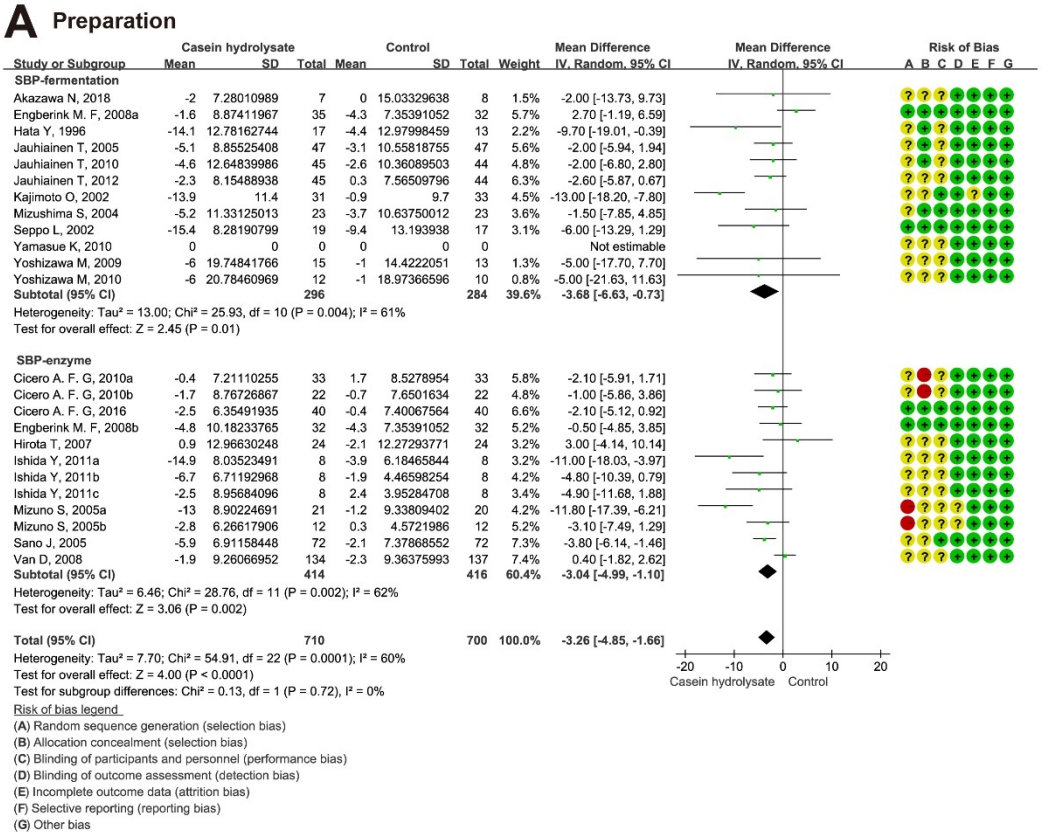
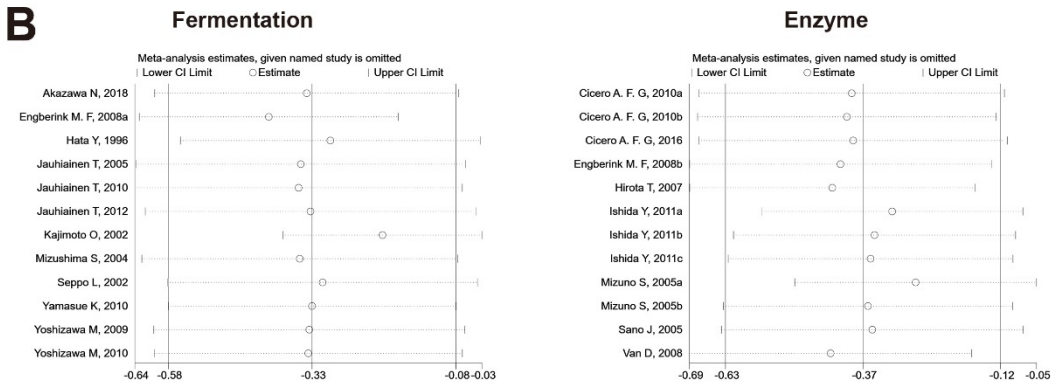


Figure S5. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on SBP (mmHg) in the duration analysis. The results represented the changes of SBP in the duration subgroup with the casein hydrolysate intervention in comparison with the control diet.





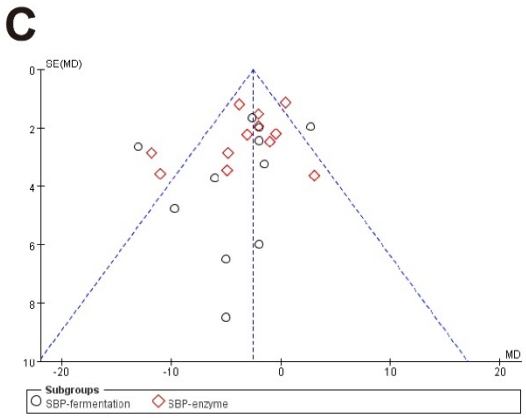
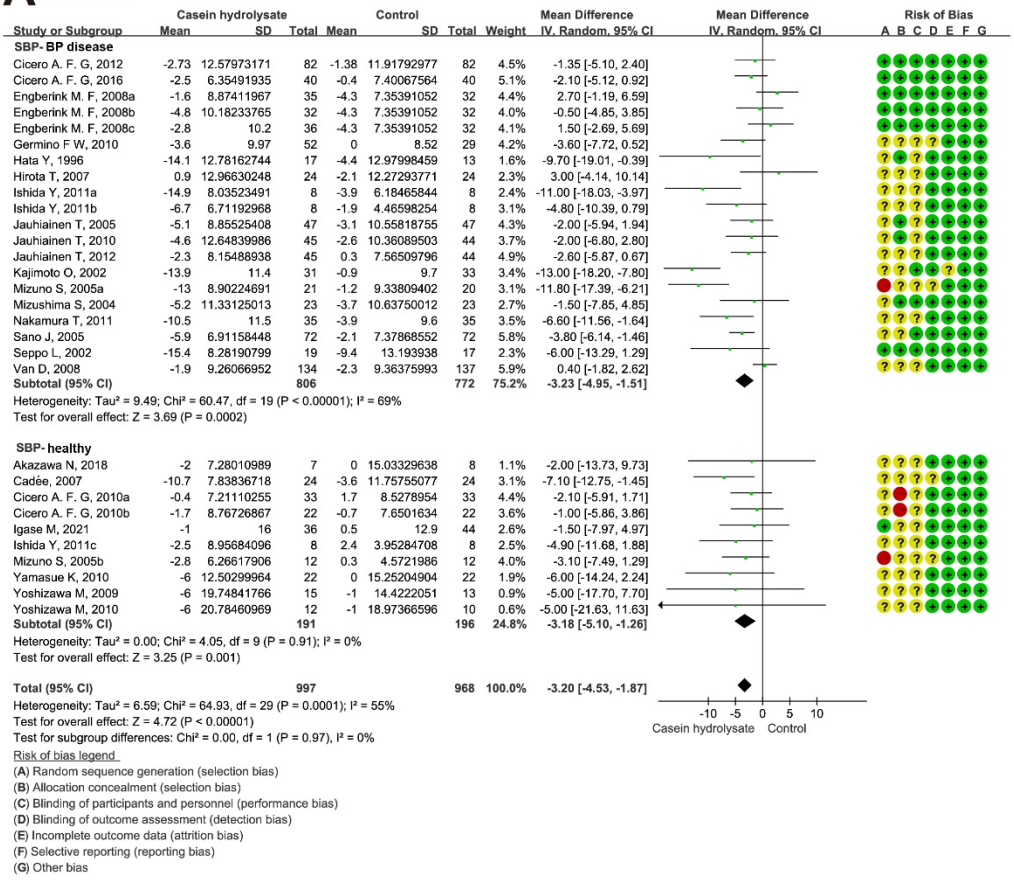


Figure S6. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on SBP (mmHg) in the preparation analysis. The results represented the changes of SBP in the preparation subgroup with the casein hydrolysate intervention in comparison with the control diet.

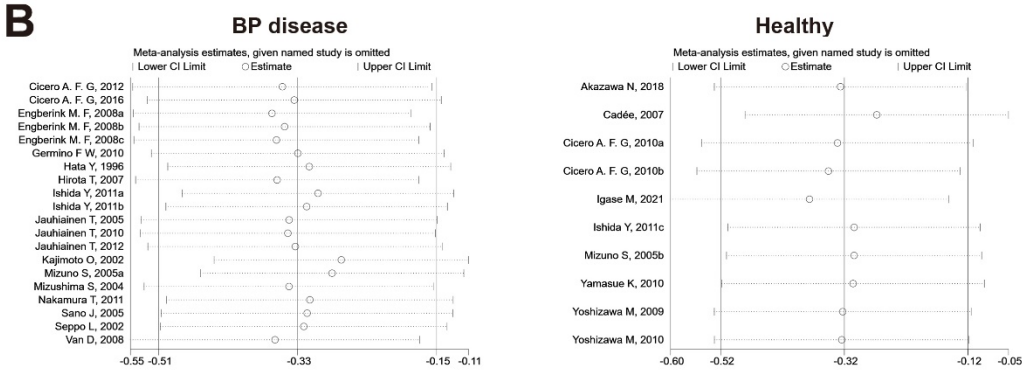
A Disease



Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

B



C

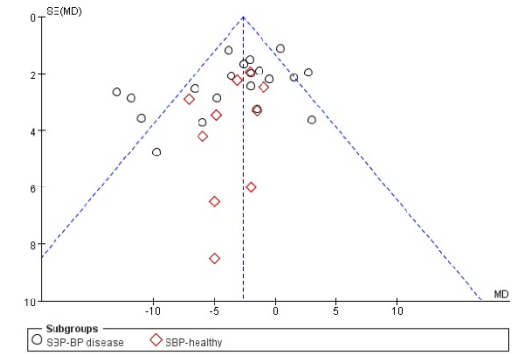
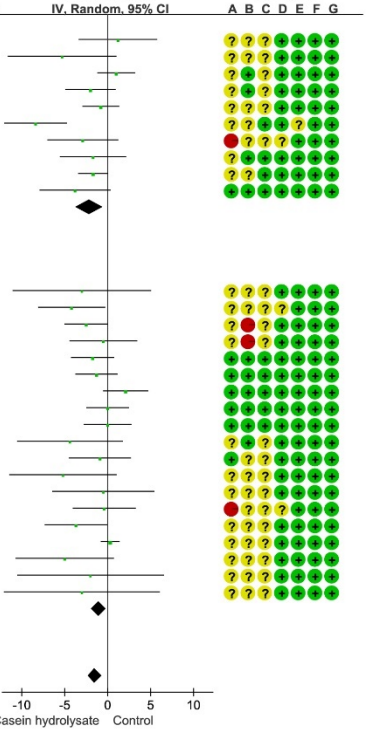


Figure S7. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on SBP (mmHg) in the disease analysis. The results represented the changes of SBP in the disease subgroup with the casein hydrolysate intervention in comparison with the control diet.

A Baseline DBP

Study or Subgroup	Casein hydrolysate Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
DBP≥90mmHg								
Hirota T, 2007	0.3	8.21735967	24	-0.9	7.92275205	24	2.4%	1.20 [-3.37, 5.77]
Ishida Y, 2011a	-7.1	6.45600496	8	-1.8	6.4501938	8	1.4%	-5.30 [-11.62, 1.02]
Jauhiainen T, 2005	-1.1	5.27909378	47	-2.1	5.61968047	47	5.7%	1.00 [-1.20, 3.20]
Jauhiainen T, 2010	-3.7	7.98846307	45	-1.7	6.05207836	44	4.3%	-2.00 [-4.94, 0.94]
Jauhiainen T, 2012	-1.6	4.99278942	45	-0.8	5.26267684	44	5.8%	-0.80 [-2.93, 1.33]
Kajimoto O, 2002	-9.1	7.5	31	-0.7	7.4	33	3.3%	-8.40 [-12.05, -4.75]
Mizuno S, 2005a	-4.2	7.61183289	21	-1.3	5.78705452	20	2.8%	-2.90 [-7.03, 1.23]
Mizushima S, 2004	-2	4.50937505	23	-0.3	8.32500009	23	3.0%	-1.70 [-5.57, 2.17]
Sano J, 2005	-3.2	5.05618433	72	-1.5	5.65022124	72	6.7%	-1.70 [-3.45, 0.05]
Seppo L, 2002	-9.3	4.79478884	19	-5.5	7.42159013	17	2.7%	-3.80 [-7.93, 0.33]
Subtotal (95% CI)			**335**			**332**	**38.0%**	**-2.10 [-3.71, -0.49]**
Heterogeneity: Tau² = 3.75; Chi² = 23.50, df = 9 (P = 0.005); I² = 62%								
Test for overall effect: Z = 2.56 (P = 0.01)								
DBP<90mmHg								
Akazawa N, 2018	-1	5.52268051	7	2	10.04987562	8	0.9%	-3.00 [-11.08, 5.08]
Cadée, 2007	-6.9	5.87877538	24	-2.7	7.83836718	24	3.0%	-4.20 [-8.12, -0.28]
Cicero A. F. G, 2010a	-1.3	6.06671245	33	1.2	4.1575233	33	5.0%	-2.50 [-5.01, 0.01]
Cicero A. F. G, 2010b	-1.2	7.00285656	22	-0.7	6.35177141	22	2.9%	-0.50 [-4.45, 3.45]
Cicero A. F. G, 2012	-2.35	8.32164046	82	-0.6	8.07902531	82	5.0%	-1.75 [-4.26, 0.76]
Cicero A. F. G, 2016	-1.2	5.85021367	40	0.1	5.40092585	40	5.1%	-1.30 [-3.77, 1.17]
Engberink M. F, 2008a	-0.3	5.91607978	35	-2.4	5.09116882	32	4.8%	2.10 [-0.54, 4.74]
Engberink M. F, 2008b	-2.4	5.09116882	32	-2.4	5.09116882	32	5.1%	0.00 [-2.49, 2.49]
Engberink M. F, 2008c	-2.4	6.6	36	-2.4	5.09116882	32	4.5%	0.00 [-2.79, 2.79]
Hata Y, 1996	-6.6	10.30776406	17	-2.2	6.85054742	13	1.5%	-4.40 [-10.55, 1.75]
Igase M, 2021	1.9	7.9	36	2.8	8.6	44	3.3%	-0.90 [-4.52, 2.72]
Ishida Y, 2011b	-4.1	6.13514466	8	1.1	6.6370174	8	1.4%	-5.20 [-11.46, 1.06]
Ishida Y, 2011c	-0.1	6.83117852	8	0.4	5.1623638	8	1.6%	-0.50 [-6.43, 5.43]
Mizuno S, 2005b	-1.4	5.38934133	12	-1	3.59026461	12	3.2%	-0.40 [-4.06, 3.26]
Nakamura T, 2011	-4.7	8.7	35	-1	6.7	35	3.3%	-3.70 [-7.34, -0.06]
Van D, 2008	-0.8	4.63033476	134	-1.1	4.68187996	137	8.2%	0.30 [-0.81, 1.41]
Yamasue K, 2010	-4	10.25597387	22	1	9.10878697	22	1.7%	-5.00 [-10.73, 0.73]
Yoshizawa M, 2009	-4	9.87420883	15	-2	12.74754878	13	0.8%	-2.00 [-10.54, 6.54]
Yoshizawa M, 2010	-2	10.39230485	12	1	11.18033989	10	0.7%	-3.00 [-12.09, 6.09]
Subtotal (95% CI)			**610**			**607**	**62.0%**	**-1.03 [-1.88, -0.17]**
Heterogeneity: Tau² = 0.67; Chi² = 22.78, df = 18 (P = 0.20); I² = 21%								
Test for overall effect: Z = 2.35 (P = 0.02)								
Total (95% CI)			**945**			**939**	**100.0%**	**-1.50 [-2.31, -0.69]**
Heterogeneity: Tau² = 1.75; Chi² = 48.97, df = 28 (P = 0.008); I² = 43%								
Test for overall effect: Z = 3.63 (P = 0.0003)								
Test for subgroup differences: Chi² = 1.34, df = 1 (P = 0.25), I² = 25.1%								

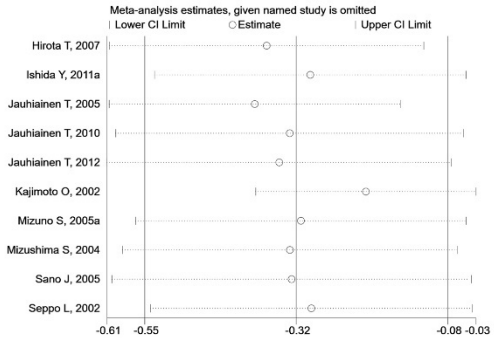


Risk of bias legend

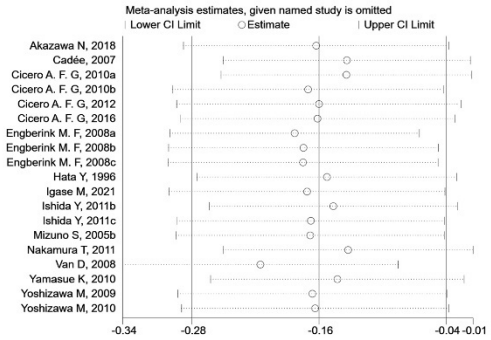
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

B

DBP ≥ 90 mmHg



DBP < 90 mmHg



C

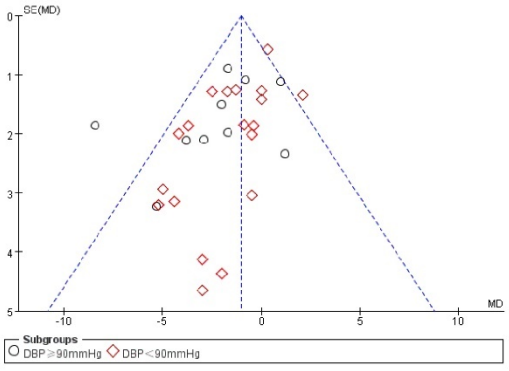
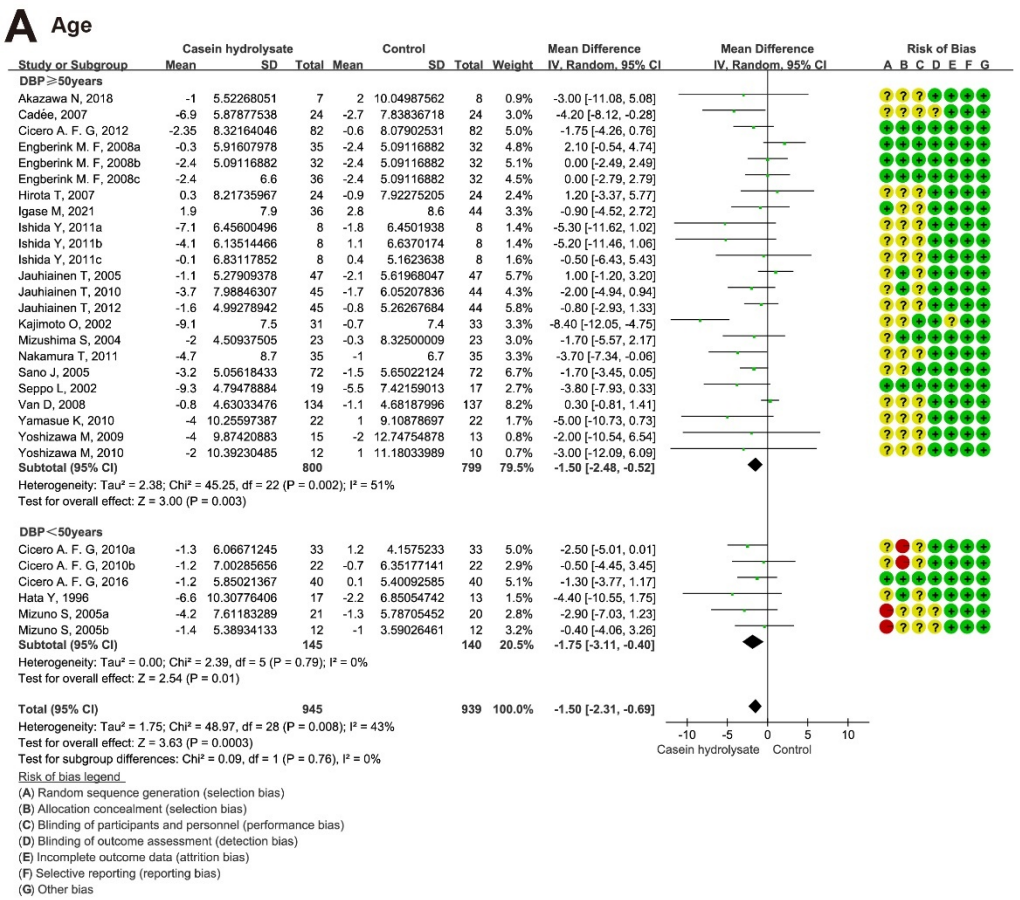
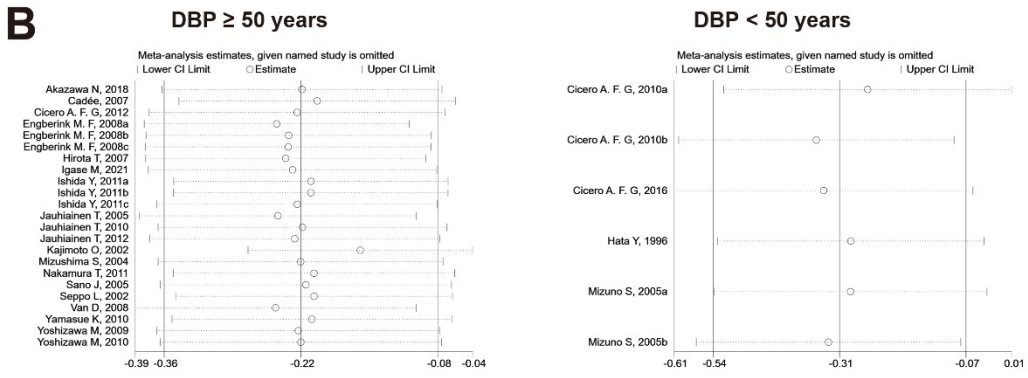


Figure S8. Forest plots (A), sensitivity analyses (B), and funnel plots (C) on DBP (mmHg) in baseline DBP analysis. The results represented the changes of DBP in baseline DBP subgroup with the casein hydrolysate intervention in comparison with the control diet.





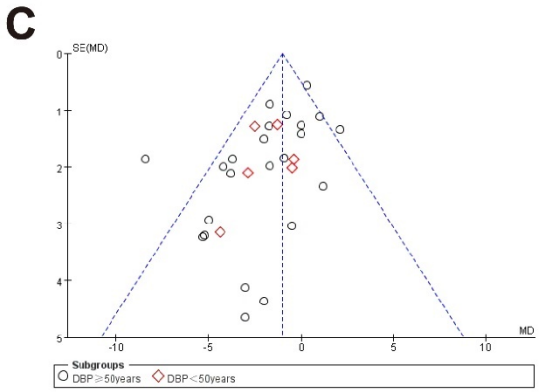


Figure S9. Forest plots (A), sensitivity analyses (B), and funnel plots (C) on DBP (mmHg) in the age analysis. The results represented the changes of DBP in the age subgroup with the casein hydrolysate intervention in comparison with the control diet.

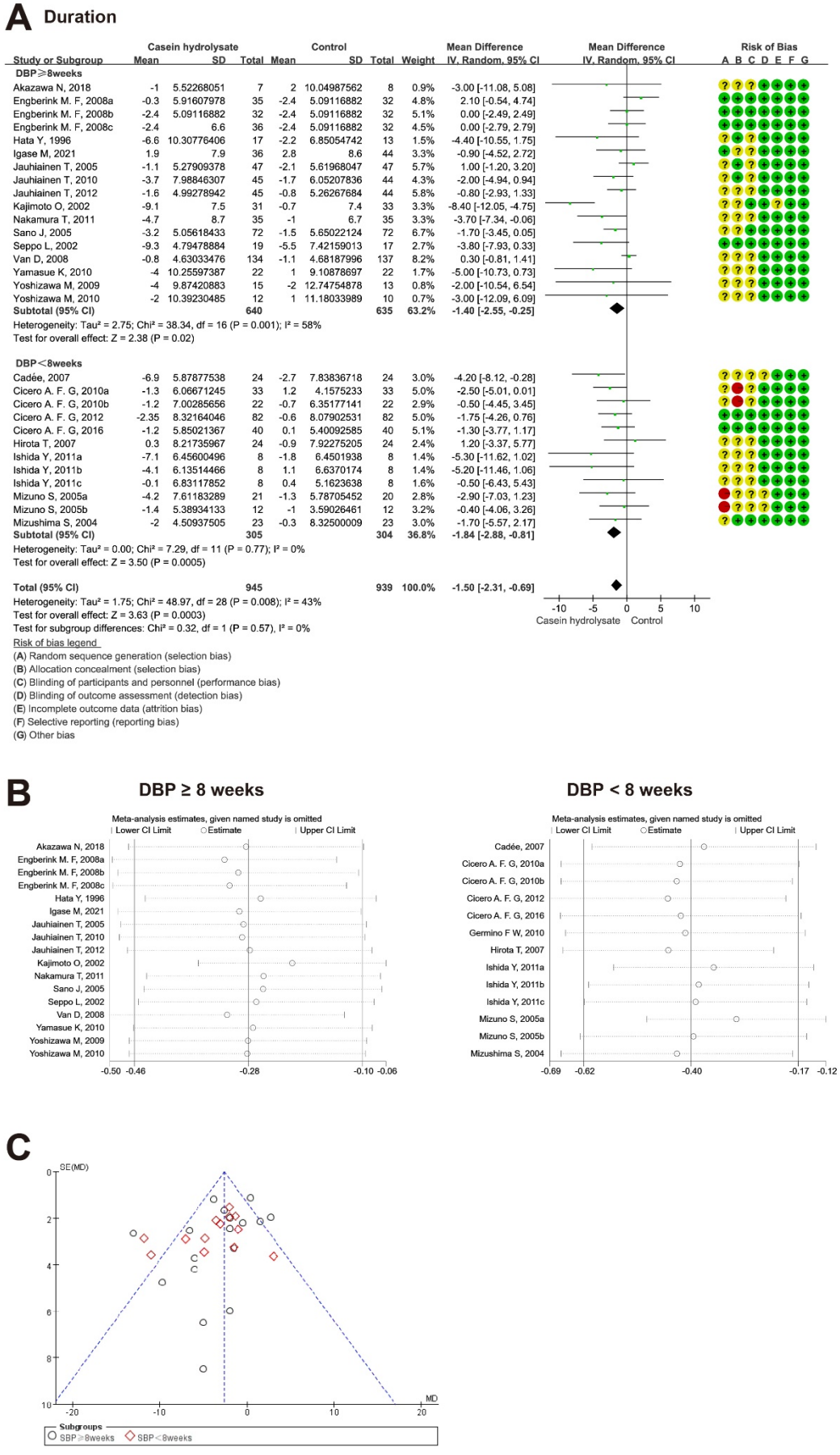
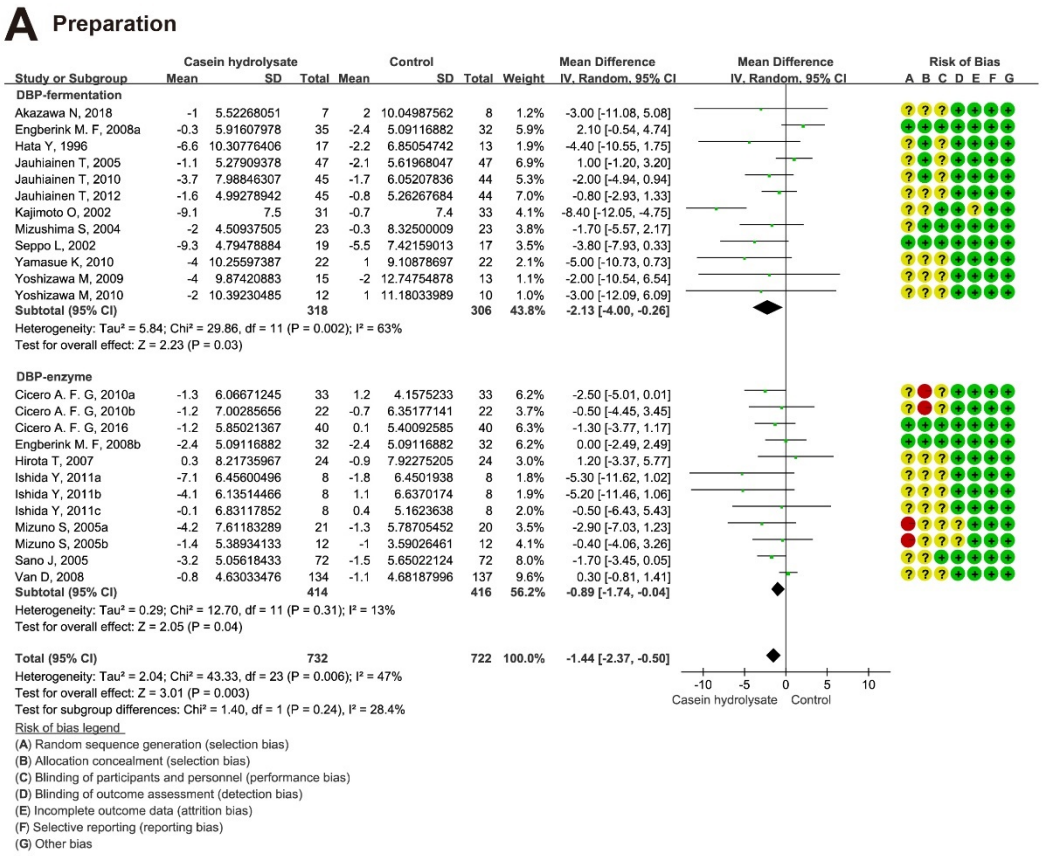
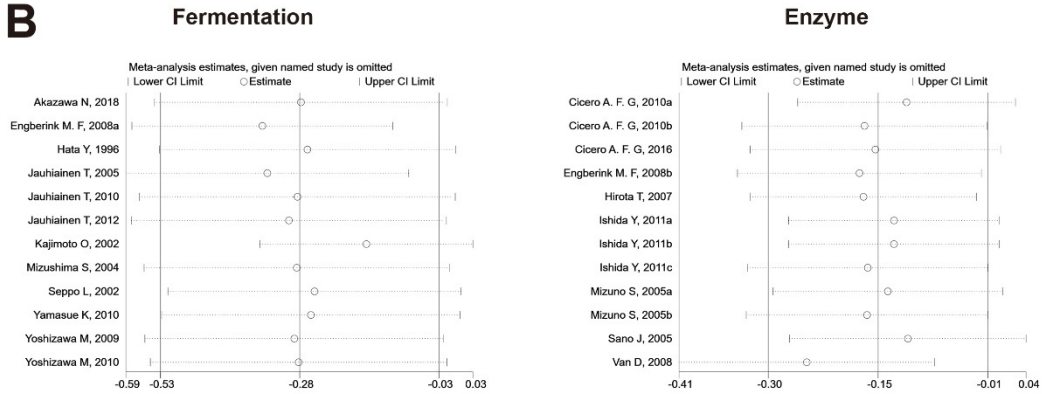


Figure S10. Forest plots (A), sensitivity analyses (B), and funnel plots (C) on DBP (mmHg) in the duration analysis. The results represented the changes of DBP in the duration subgroup with the casein hydrolysate intervention in comparison with the control diet.





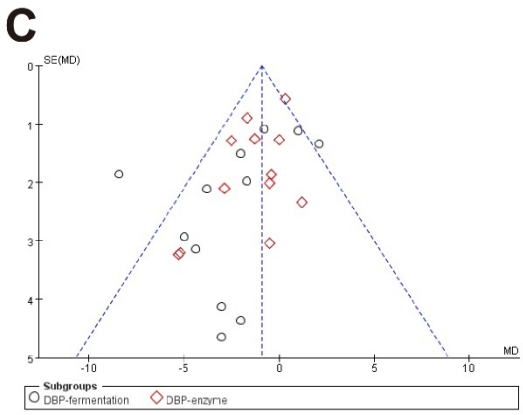


Figure S11. Forest plots (A), sensitivity analyses (B), and funnel plots (C) on DBP (mmHg) in the preparation analysis. The results represented the changes of DBP in the preparation subgroup with the casein hydrolysate intervention in comparison with the control diet.

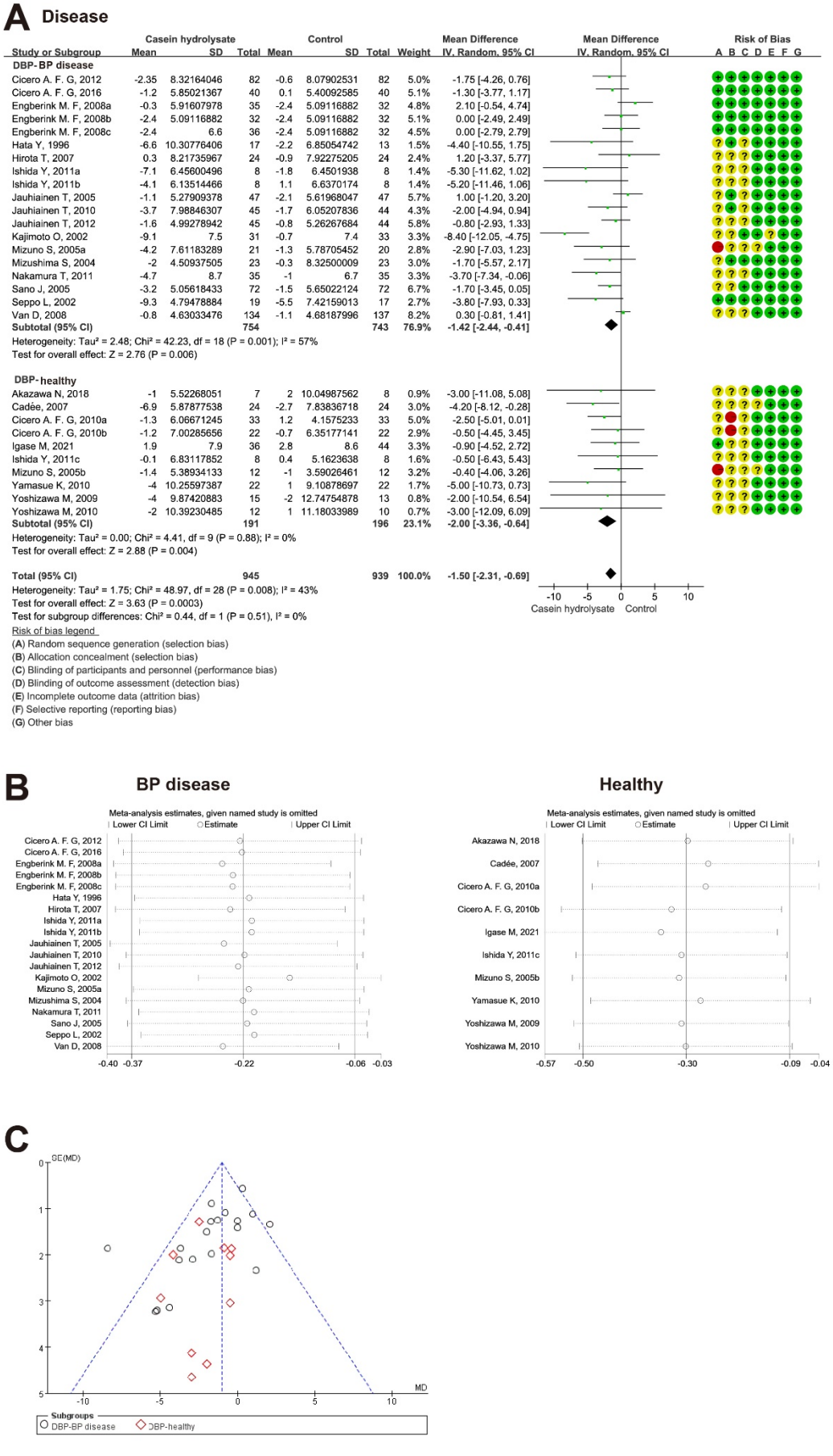


Figure S12. Forest plots (A), sensitivity analyses (B), and funnel plots (C) on DBP (mmHg) in the disease analysis. The results represented the changes of DBP in the disease subgroup with the casein hydrolysate intervention in comparison with the control diet.

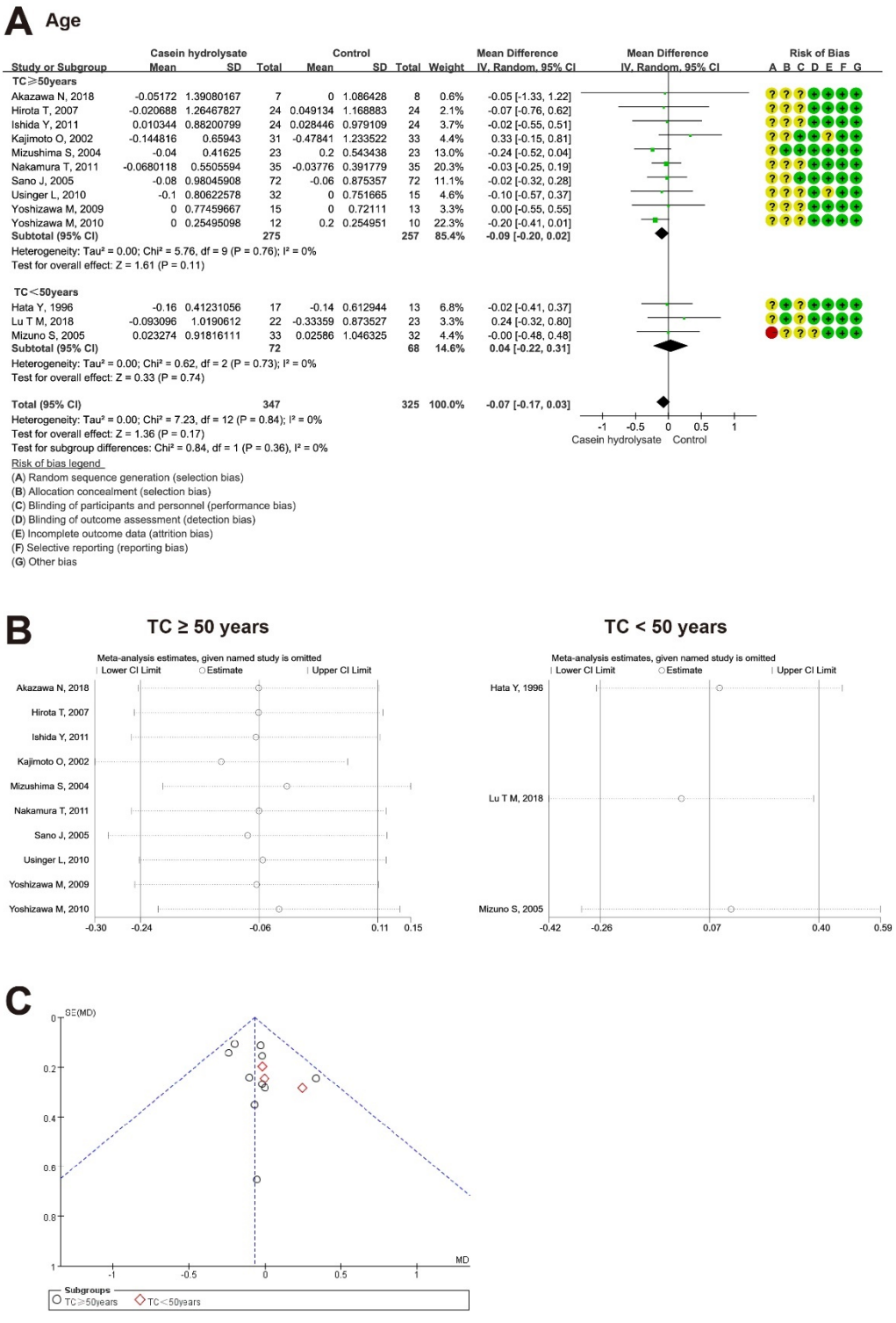


Figure S13. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on TC (mmol/L) in the age analysis. The results represented the changes of TC in the age subgroup with the casein hydrolysate intervention in comparison with the control diet.

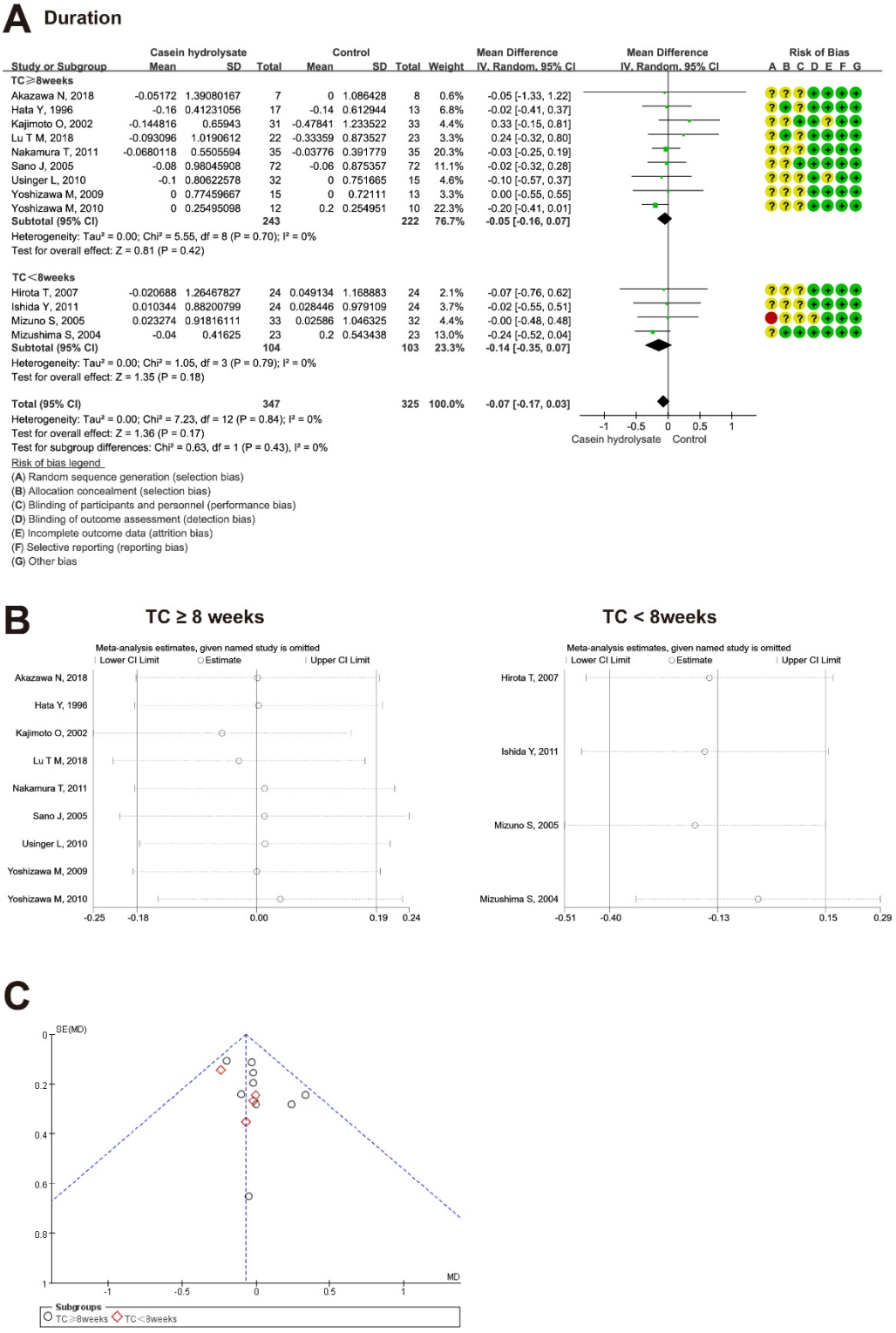


Figure S14. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on TC (mmol/L) in the duration analysis. The results represented the changes of TC in the duration subgroup with the casein hydrolysate intervention in comparison with the control diet.

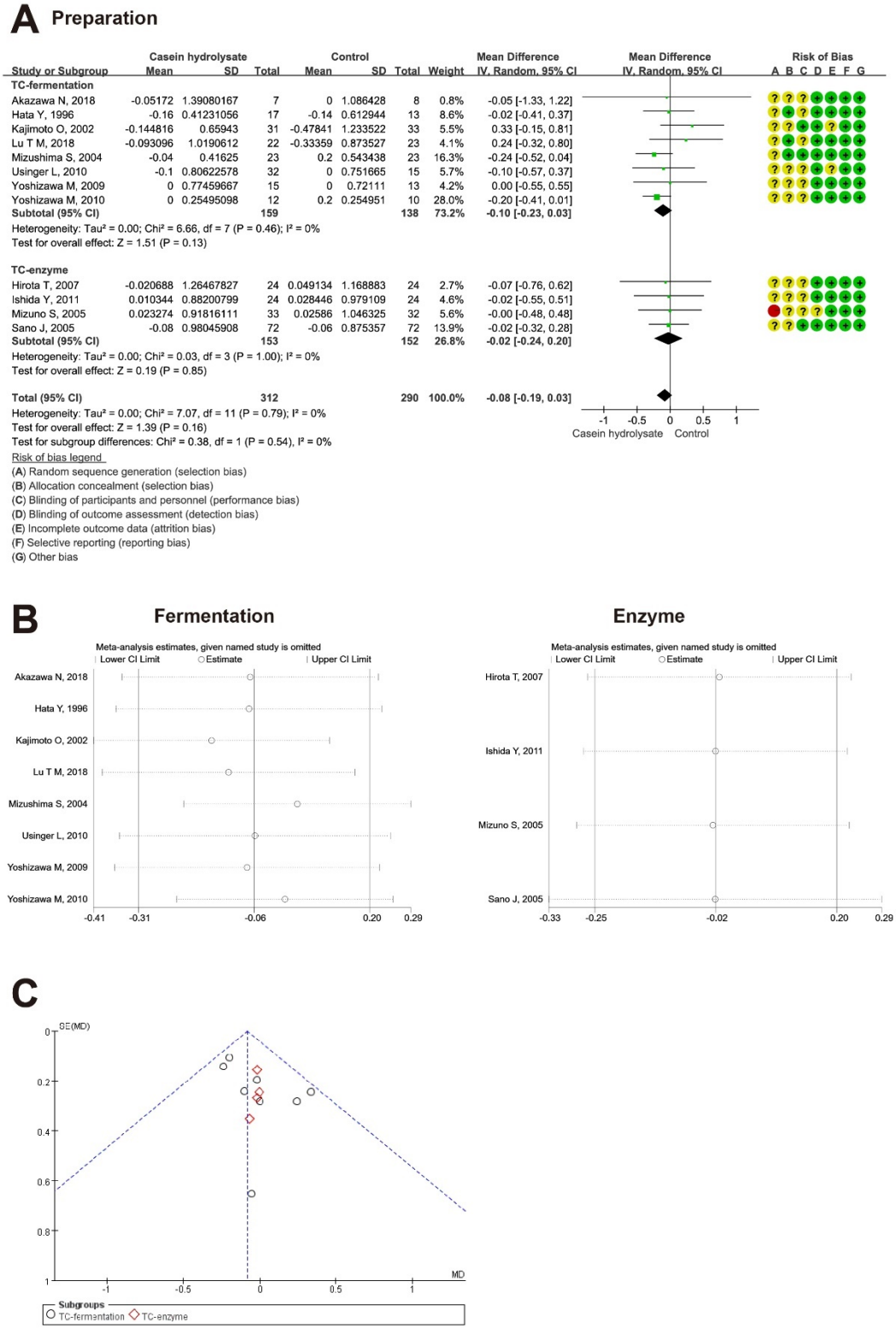
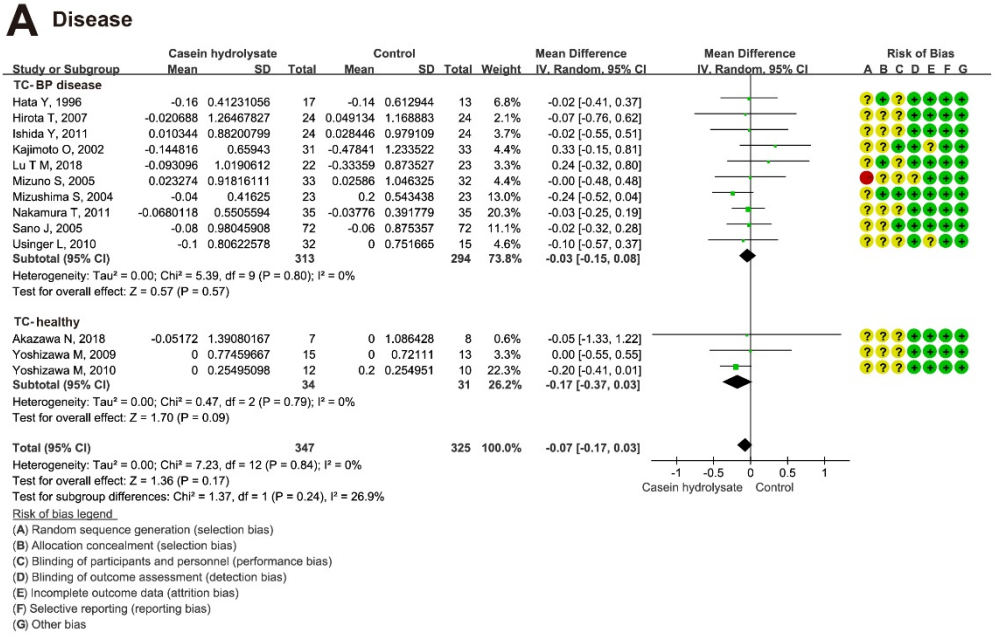
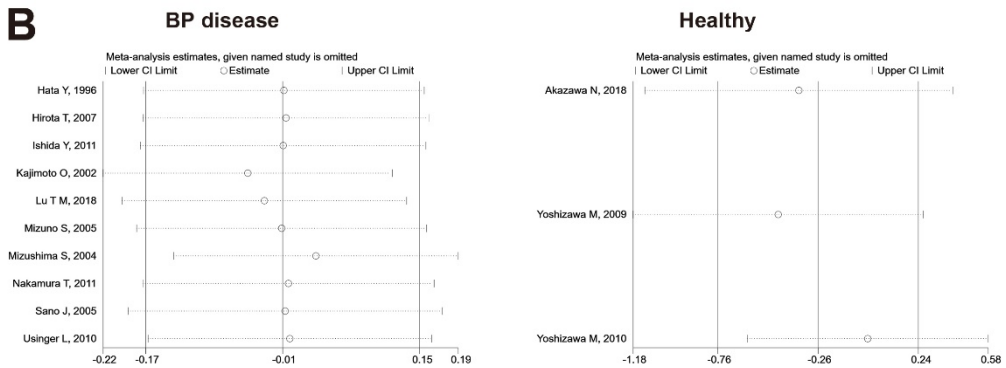


Figure S15. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on TC (mmol/L) in the preparation analysis. The results represented the changes of TC in the preparation subgroup with the casein hydrolysate intervention in comparison with the control diet.





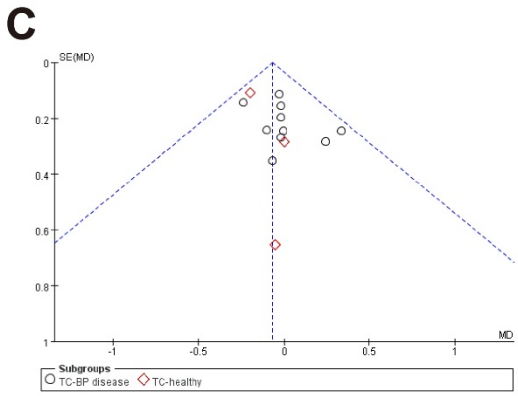


Figure S16. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on TC (mmol/L) in the disease analysis. The results represented the changes of TC in the disease subgroup with the casein hydrolysate intervention in comparison with the control diet.

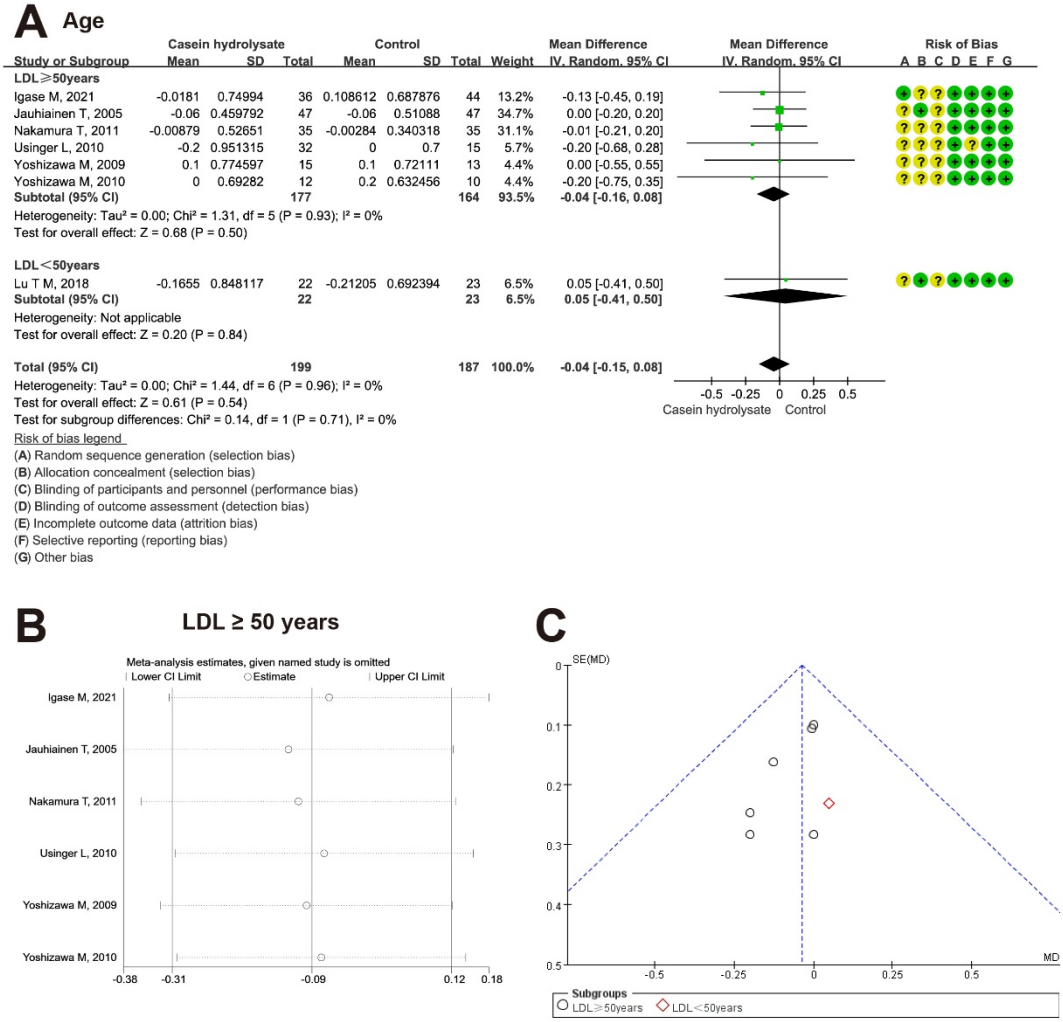


Figure S17. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on LDL (mmol/L) in the age analysis. The results represented the changes of LDL in the age subgroup with the casein hydrolysate intervention in comparison with the control diet.

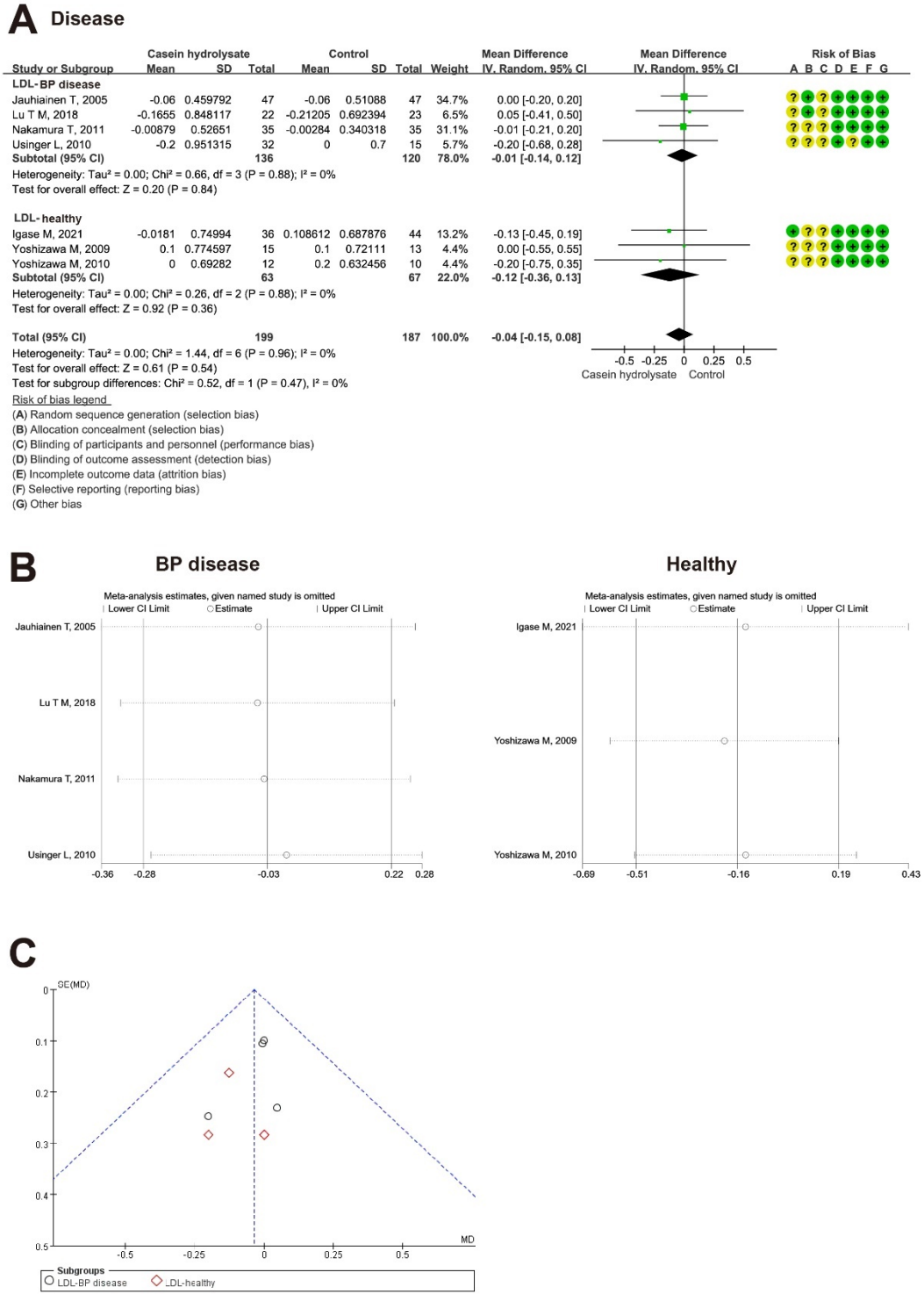
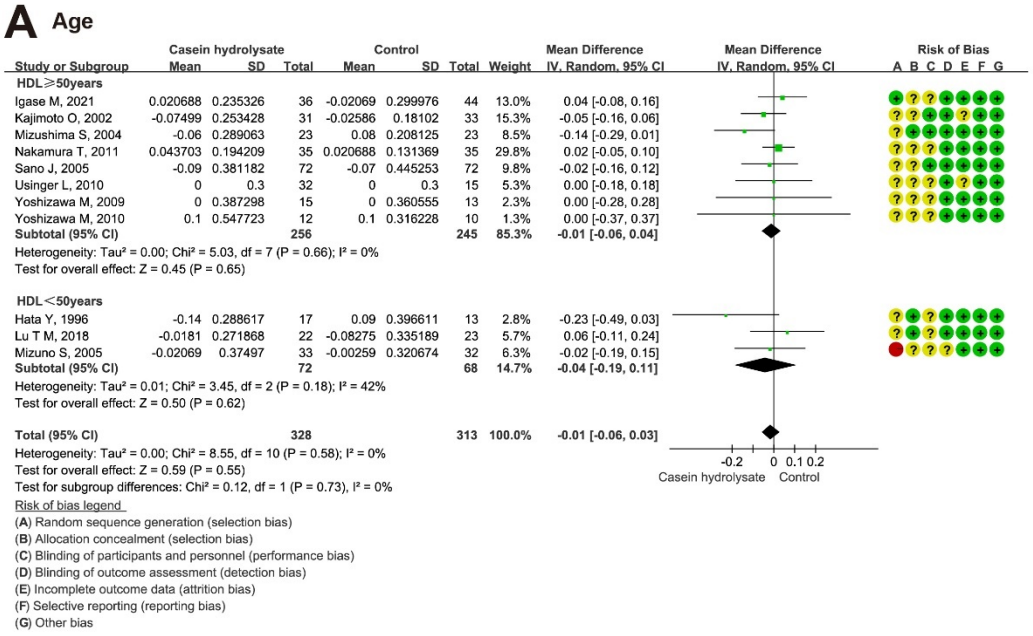
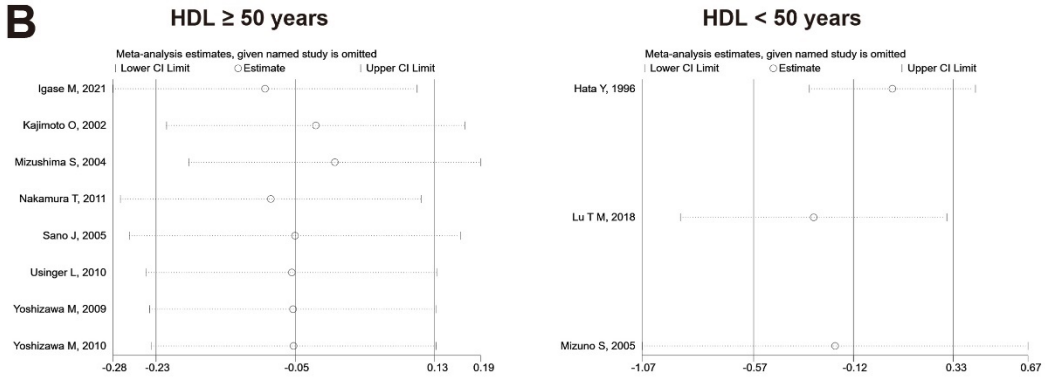


Figure S18. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on LDL (mmol/L) in the disease analysis. The results represented the changes of LDL in the disease subgroup with the casein hydrolysate intervention in comparison with the control diet.





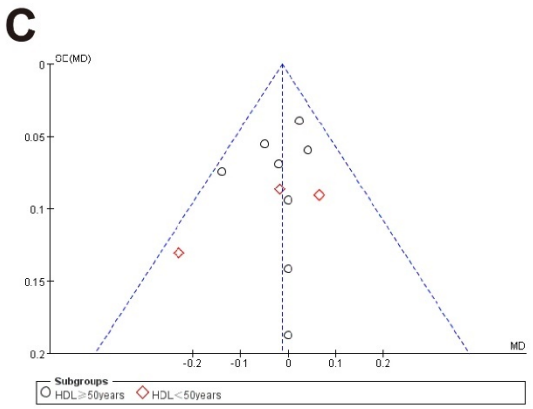


Figure S19. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on HDL (mmol/L) in the age analysis. The results represented the changes of HDL in the age subgroup with the casein hydrolysate intervention in comparison with the control diet.

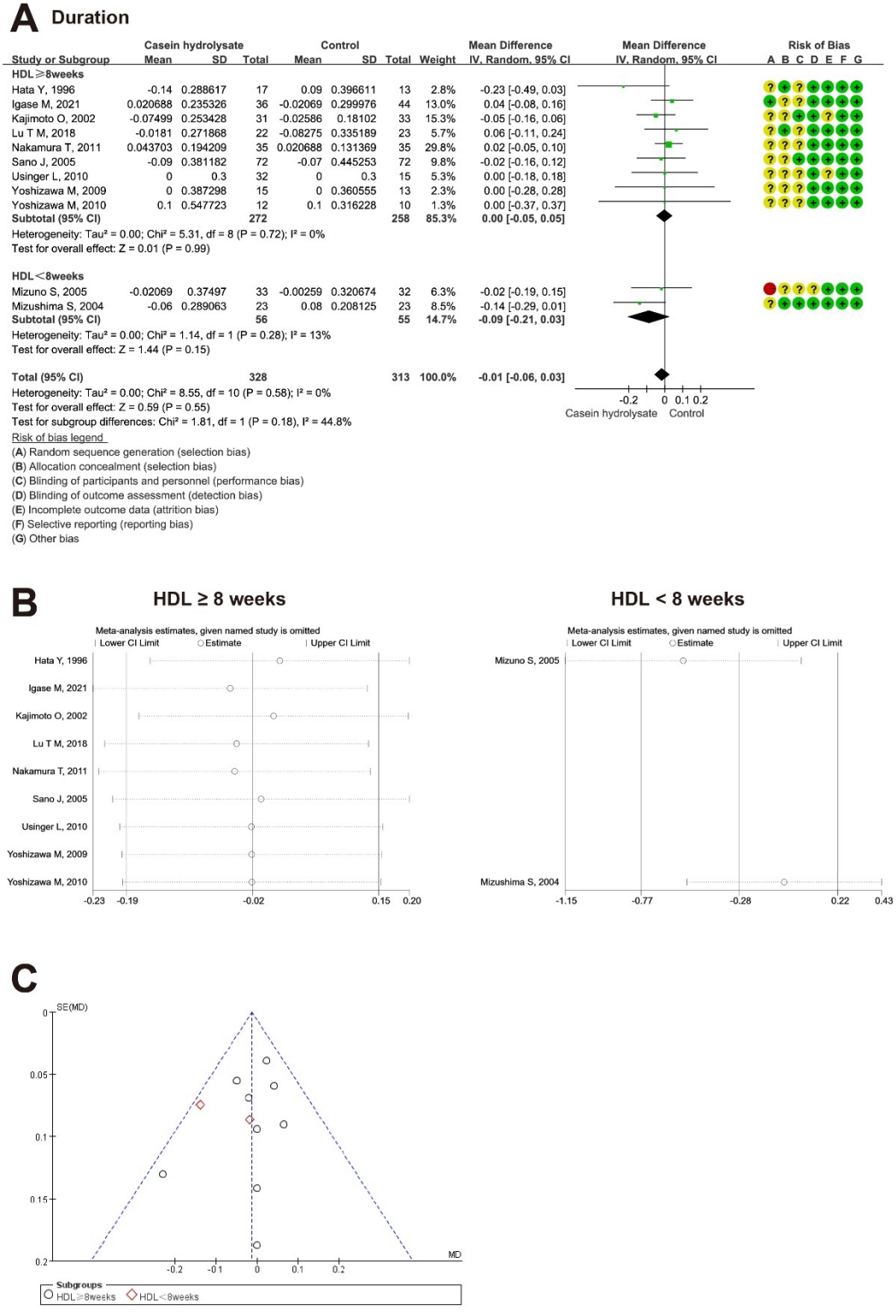


Figure S20. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on HDL (mmol/L) in the duration analysis. The results represented the changes of HDL in the duration subgroup with the casein hydrolysate intervention in comparison with the control diet.

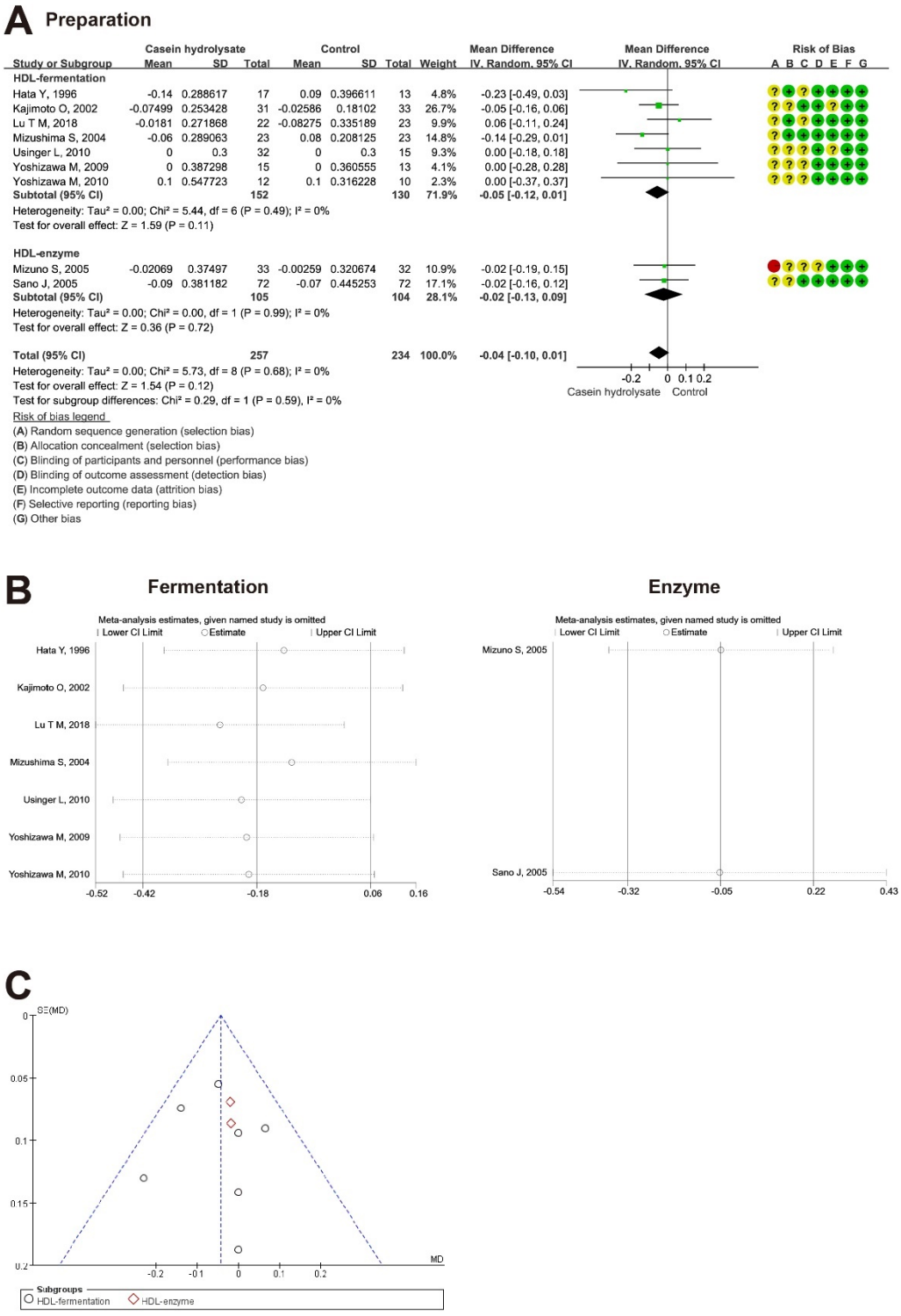


Figure S21. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on HDL (mmol/L) in the preparation analysis. The results represented the changes of HDL in the preparation subgroup with the casein hydrolysate intervention in comparison with the control diet.

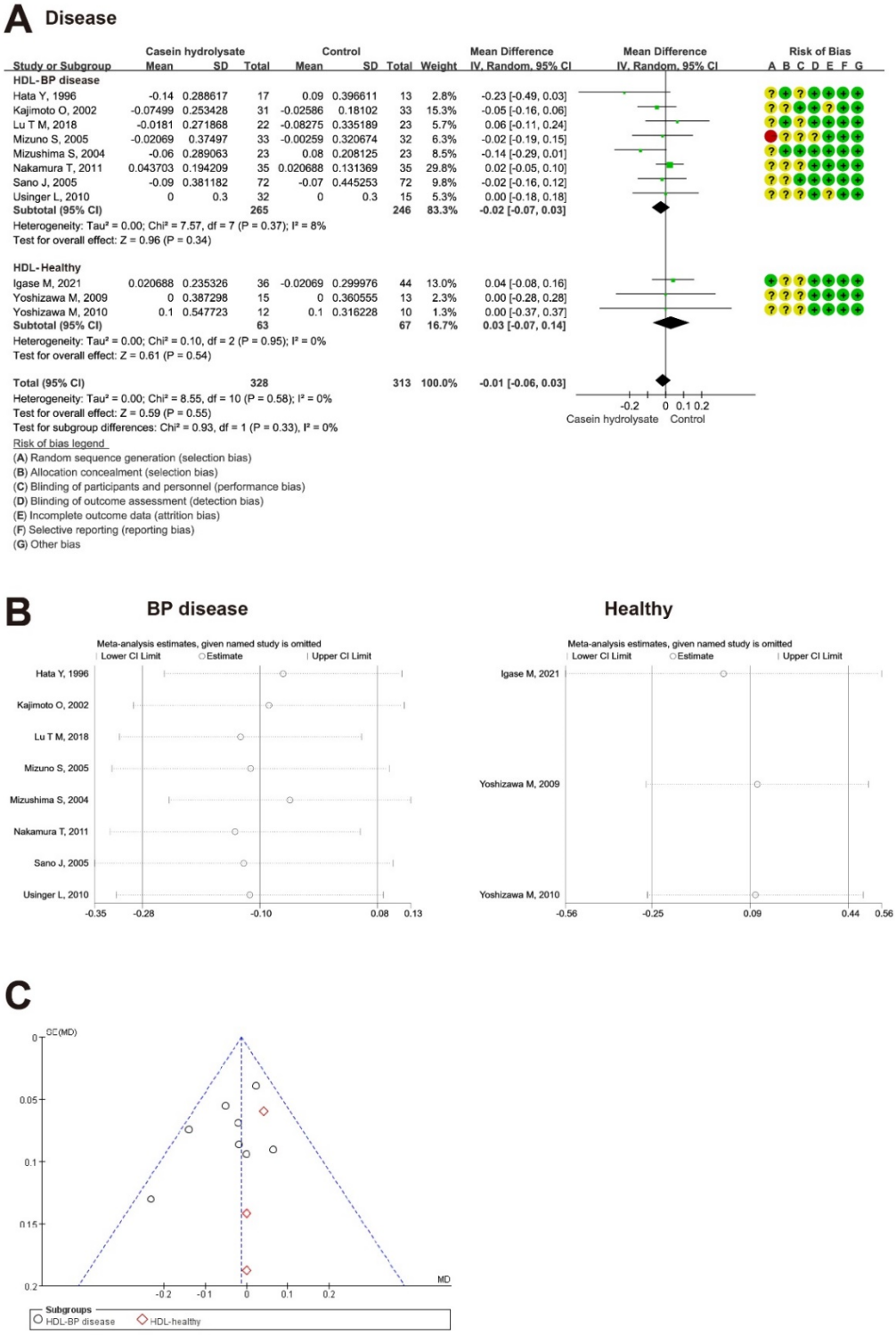
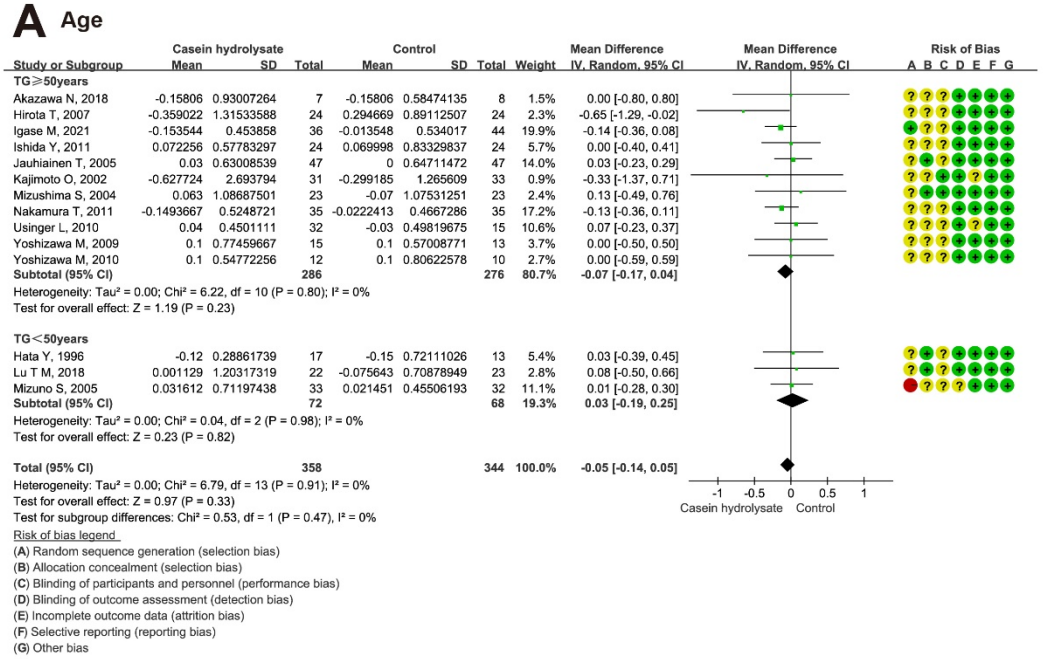
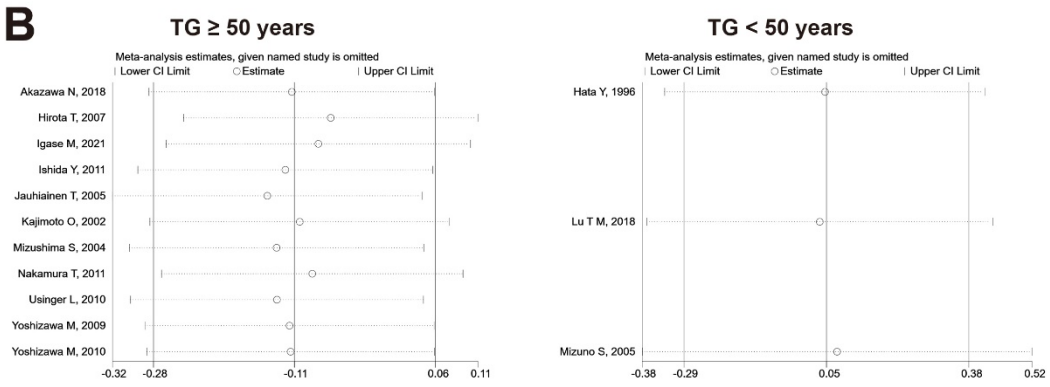


Figure S22. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on HDL (mmol/L) in the disease analysis. The results represented the changes of HDL in the disease subgroup with the casein hydrolysate intervention in comparison with the control diet.





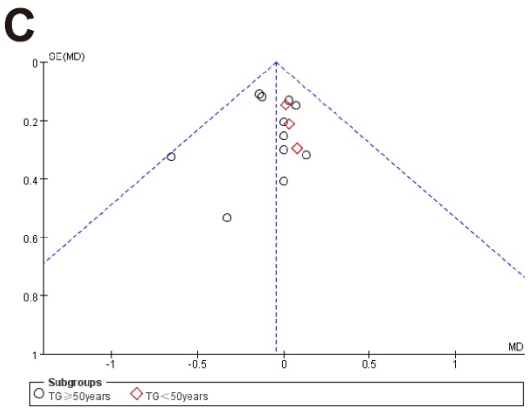
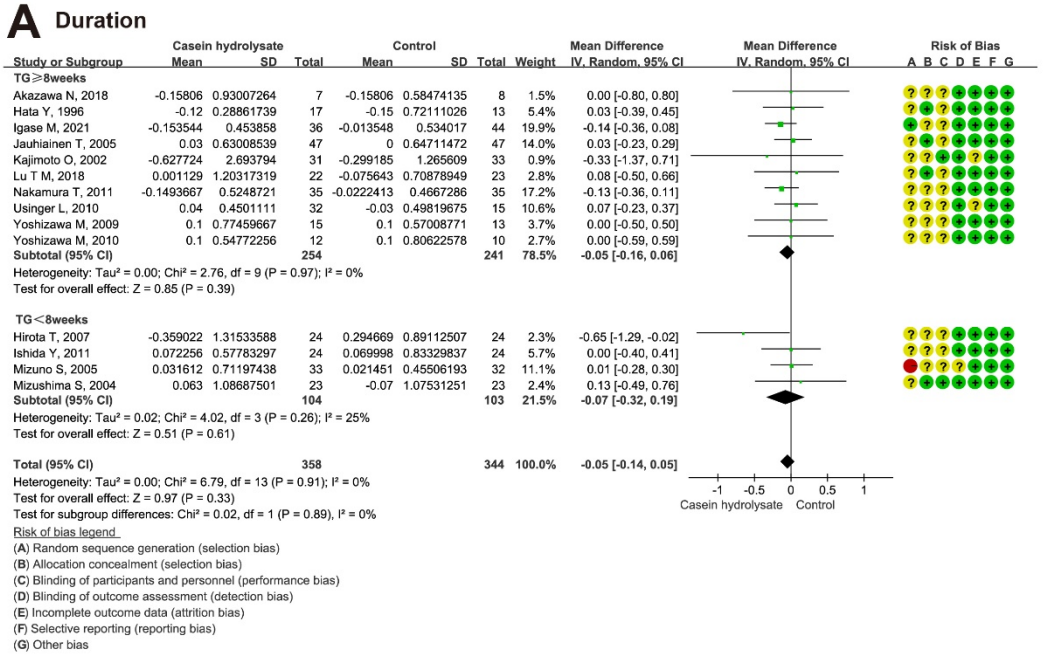
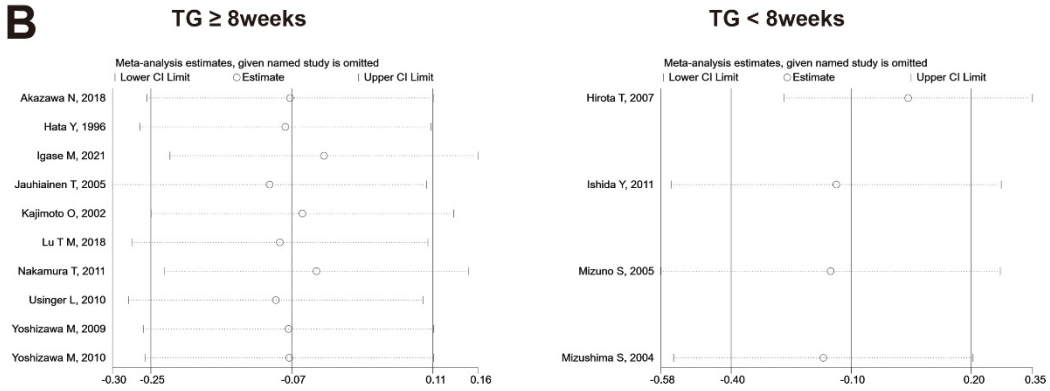


Figure S23. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on TG (mmol/L) in the age analysis**.** The results represented the changes of TG in the age subgroup with the casein hydrolysate intervention in comparison with the control diet.





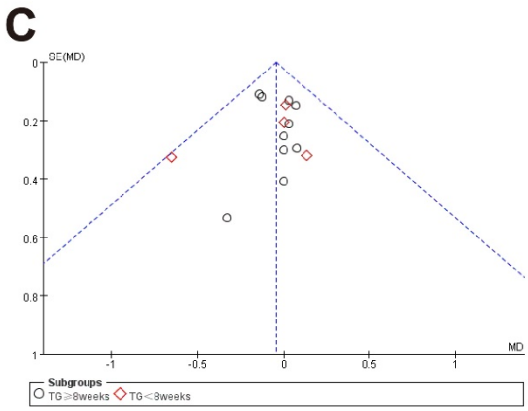


Figure S24. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on TG (mmol/L) in the duration analysis. The results represented the changes of TG in the duration subgroup with the casein hydrolysate intervention in comparison with the control diet.

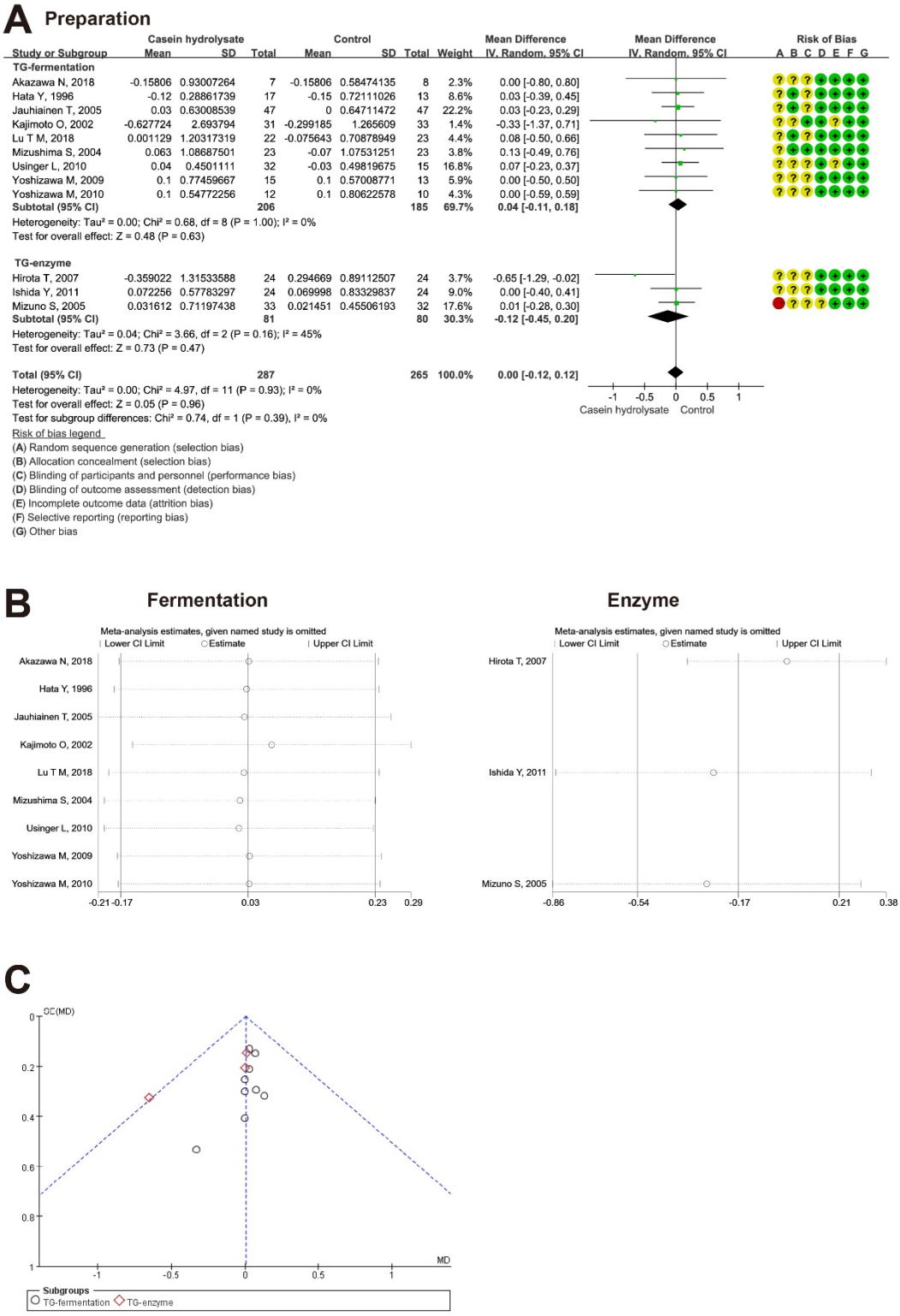
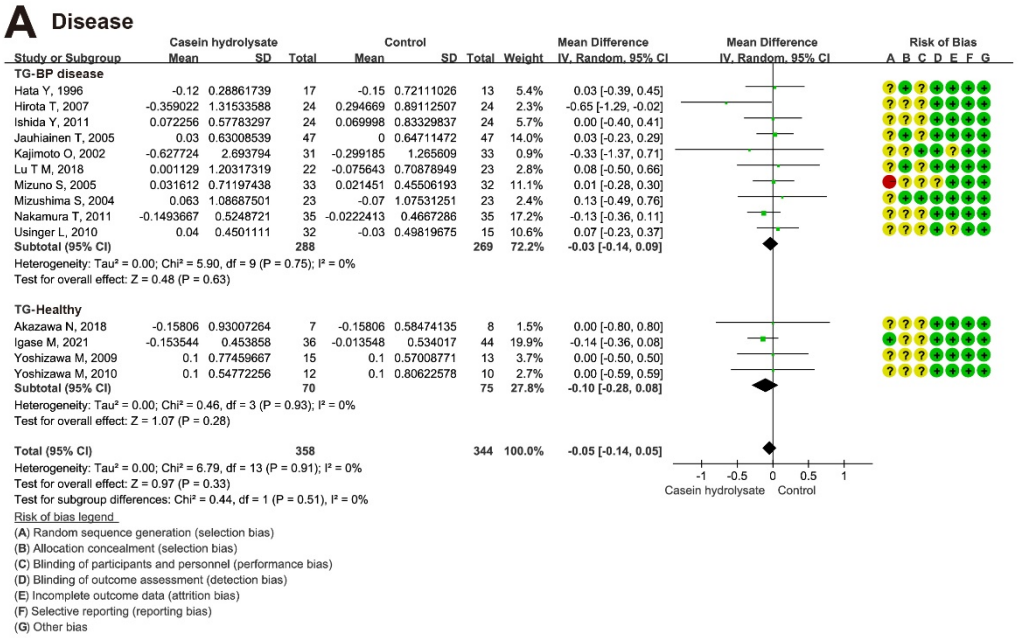
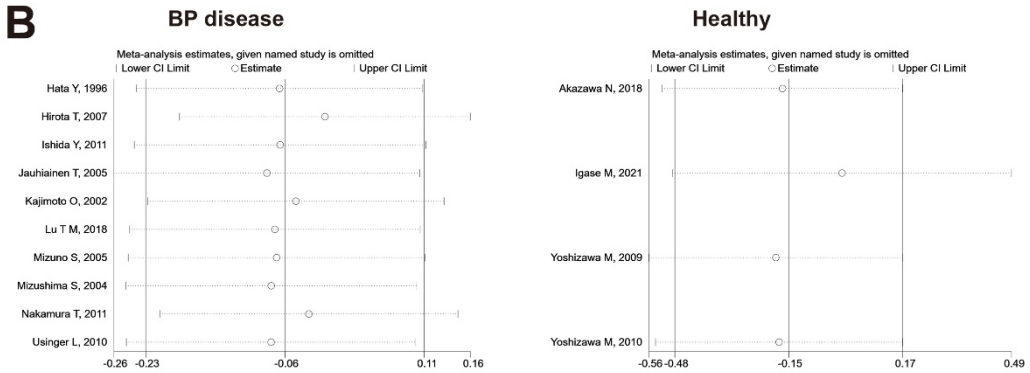


Figure S25. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on TG (mmol/L) in the preparation analysis. The results represented the changes of TG in the preparation subgroup with the casein hydrolysate intervention in comparison with the control diet.





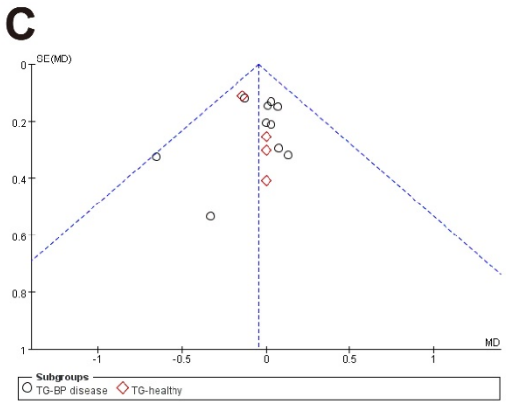
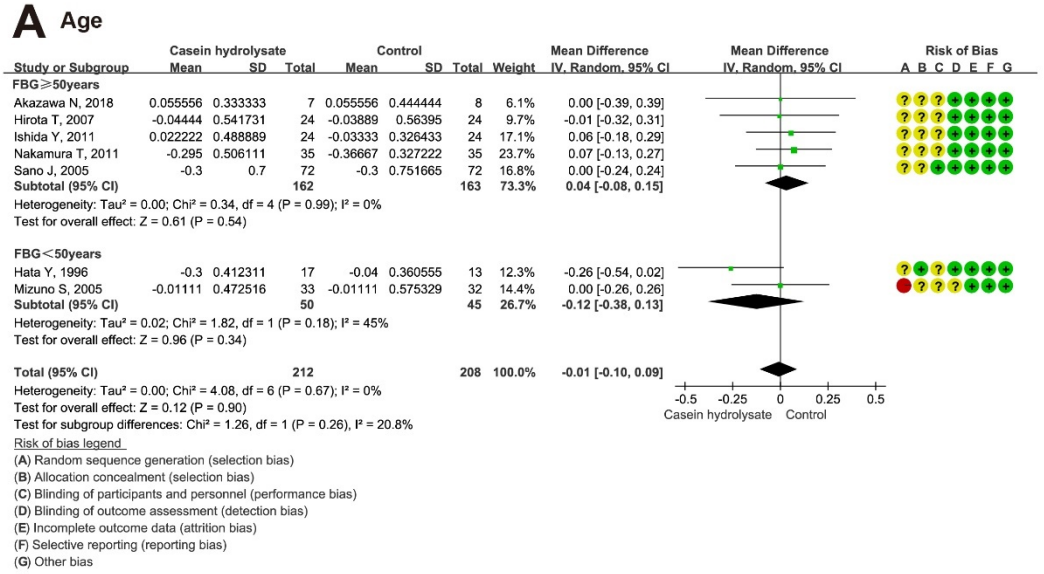
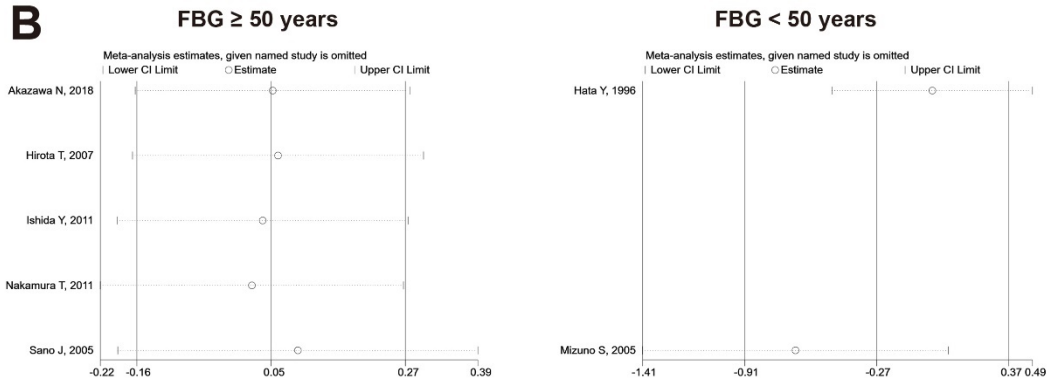


Figure S26. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on TG (mmol/L) in the disease analysis. The results represented the changes of TG in the disease subgroup with the casein hydrolysate intervention in comparison with the control diet.





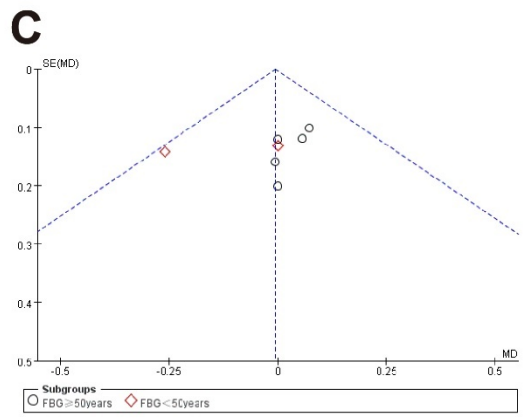
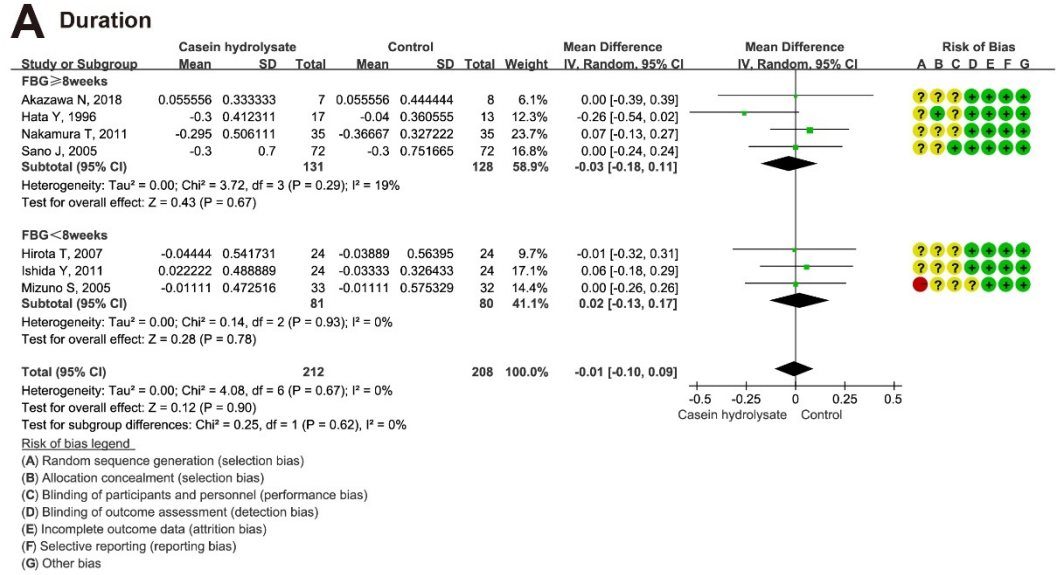
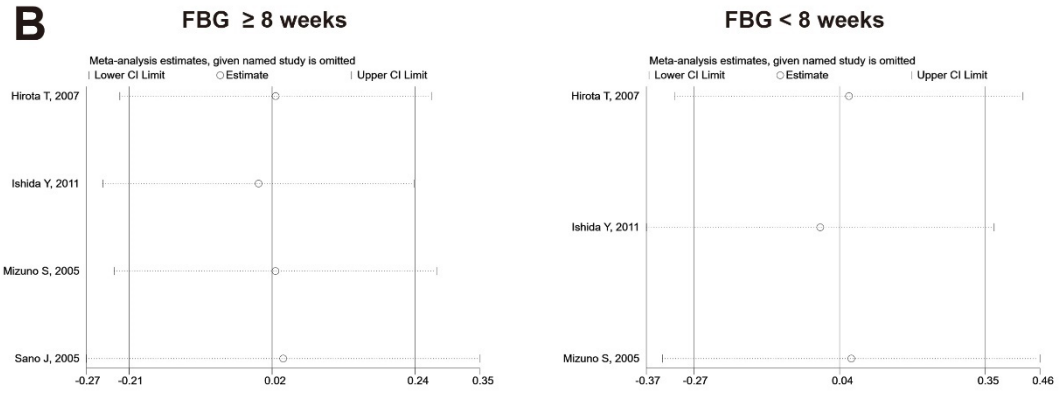


Figure S27. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on FBG (mmol/L) in the age analysis. The results represented the changes of FBG in the age subgroup with the casein hydrolysate intervention in comparison with the control diet.





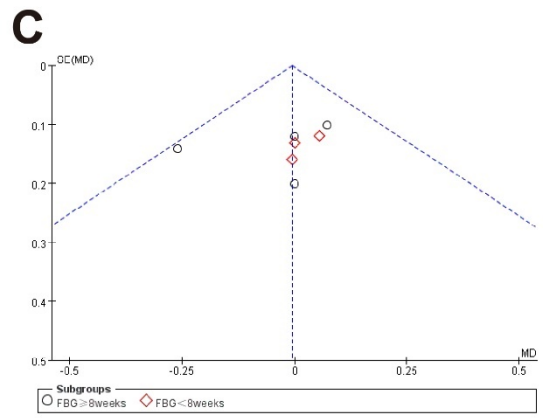
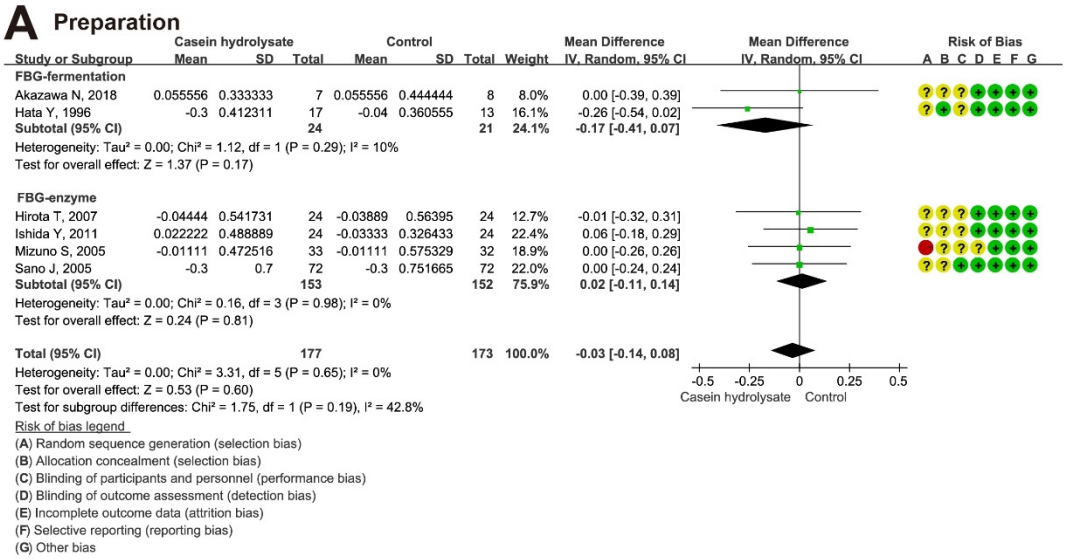
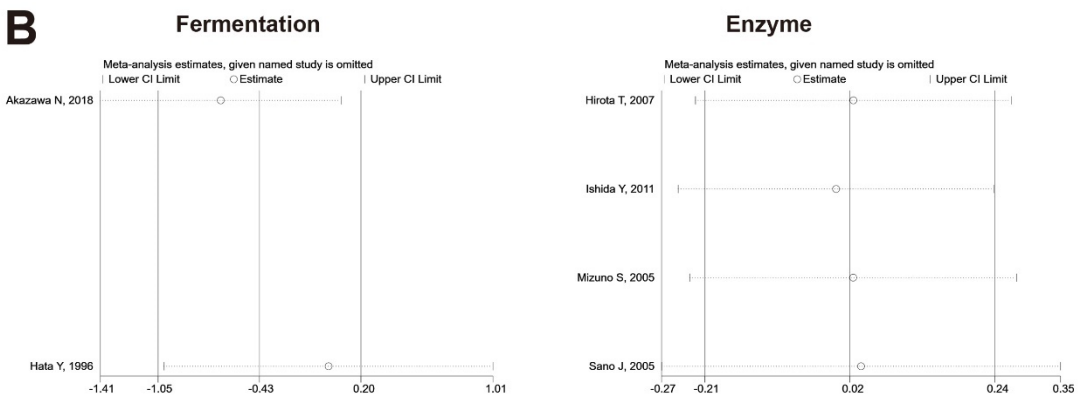


Figure S28. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on FBG (mmol/L) in the duration analysis. The results represented the changes of FBG in the duration subgroup with the casein hydrolysate intervention in comparison with the control diet.





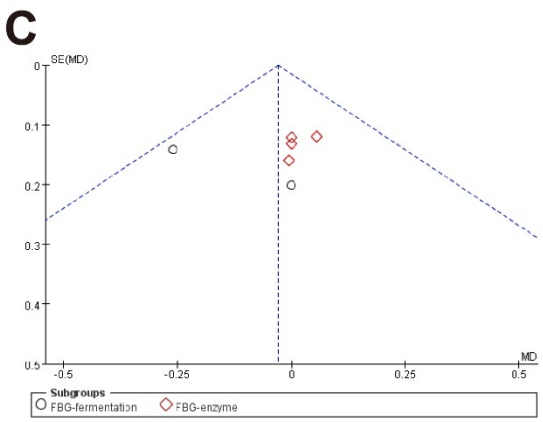


Figure S29. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on FBG (mmol/L) in the preparation analysis. The results represented the changes of FBG in the preparation subgroup with the casein hydrolysate intervention in comparison with the control diet.

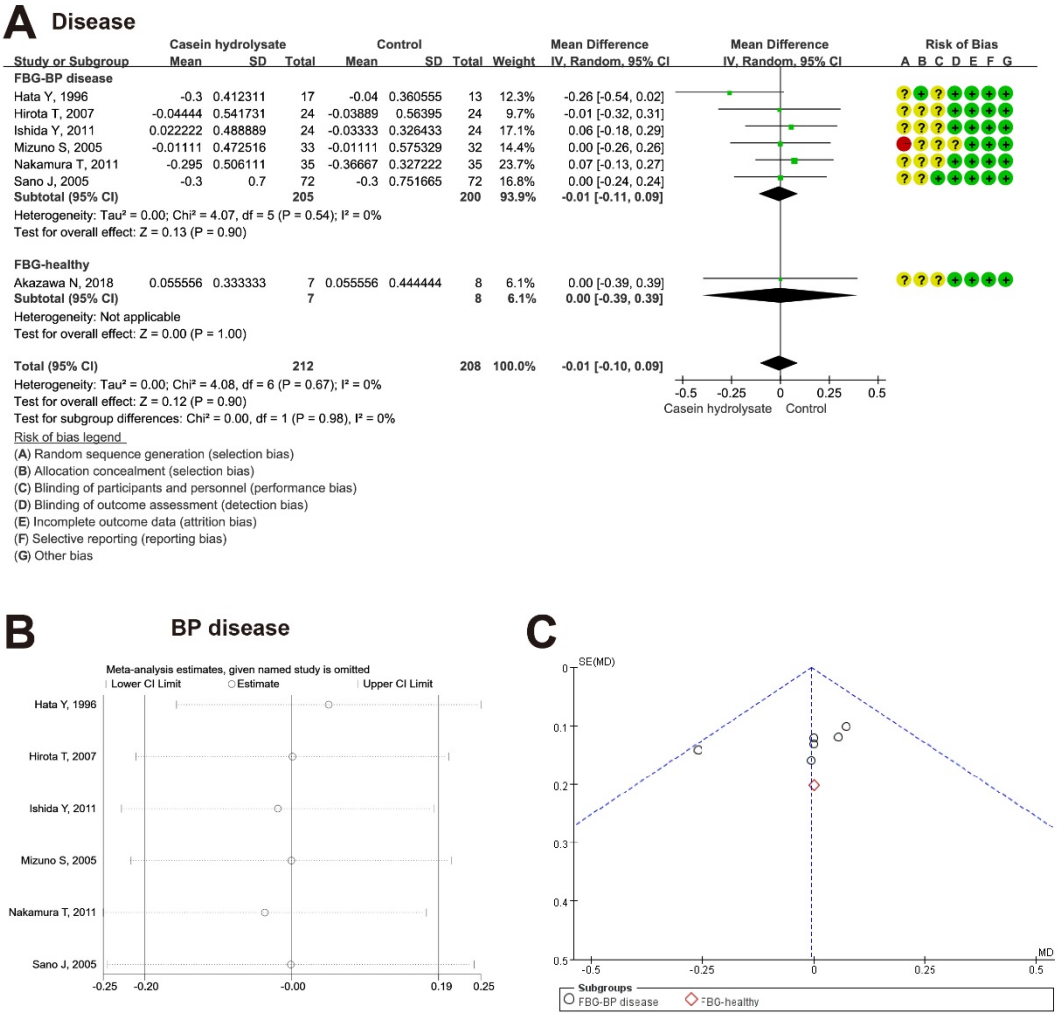


Figure S30. Forest plots (A), sensitivity analysis (B), and funnel plots (C) on FBG (mmol/L) in the disease analysis. The results represented the changes of FBG in the disease subgroup with the casein hydrolysate intervention in comparison with the control diet.