Supplementary Data

Clinical Efficacy and Safety of Anti-Obesity Medications Among Adult East Asian People with Obesity: A Systematic Literature Review and Indirect Treatment Comparison

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Tables

Table S1 Key search commands for Ovid based searches

Search commands	Explanations
/	Indicates a subject heading with all subheadings selected
Exp	Indicates that the subject heading was exploded to include the narrower, more specific terms beneath it in the tree
Mp	Defaults to the 'multi-purpose' fields, including title, original title, abstract, subject heading, name of substance.
$	Indicates that the search term was truncated (eg, wart$ searches for wart and warts)
ti,ab,kw.	Search terms in the title, abstract or author keywords, in MEDLINE/EMBASE
Adj.	Adjacent to
?	Indicates that if more than one spelling it will identify the alternative spelling, eg, Tumo?r will pick up tumor and tumour
Or/1–18	Combine search lines 1–18 with Boolean OR

Table S2 Search strategy [Embase 1974 to 2023 January 16, Ovid MEDLINE(R) ALL 1946 to January 16, 2023]

#	Searches	Results
1	exp obesity/ or exp overweight/ or weight loss/ or weight reduction/ or (obesity or obese).ti. or (weight adj2 (los* or reduc*)).ti,ab. or (overweight or over-weight or over weight or overeating or over eating or over-eating).ti.	1,232,248
2	exp semaglutide/ or semaglutide.ti,ab. or exp Mazindol/ or Mazindol.ti,ab.	6,888
3	exp randomized controlled trial/ or randomized controlled trials as topic/ or exp Randomization/ or exp clinical trial/ or double blind.ti,ab. or single blind.ti,ab. or (cross-over or crossover).ti,ab. or randomization/ or control group/ or (clin$ adj3 trial$).ti,ab. or randomi?ed controlled trial$.mp. or RCT.ti,ab. or ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).mp. or placebo$.ti,ab. or (random$ adj2 allocat$).ti,ab. or open label.ti,ab. or (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,ab. or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).mp. or randomized controlled trial.pt.	4,559,118
4	1 and 2 and 3	1,162
5	(case reports or editorial or note or letter or comment or Books or Chapter or News or review).pt. or exp case report/ or case report?.ti.	15,828,074
6	4 not 5	690
7	exp china or exp hong kong or exp japan or exp macau or exp mongolia or exp north korea or exp "democratic people's republic of korea" or exp south korea or exp "republic of korea" or exp Taiwan	1,076,597
8	(east asia or china or chinese or beijing or "chinese people's republic" or "people's republic of china" or hong kong or hongkong or japan or japanese or tokyo or macau or mongolia or "mongolian people's republic" or north korea or "democratic people's republic of korea" or "korean people's republic" or south korea or "republic of korea" or seoul or taiwan).ti,ab	1,942,914
9	7 or 8	2,208,458
10	6 and 9	28
11	limit 10 to (english or japanese)	28
12	remove duplicates from 11	19

Table S3 Search strategy for database: ICHUSHI 2022 December 12

#	Searches	Results
1	肥満症/TH or 体重減少/TH or 体重増加/TH or 肥満/TH or 肥満/TA	111,537
2	Semaglutide/TH or Semaglutide/TA or セマグルチド/TA or Mazindol/TH or Mazindol/TA or マジンドール/TA	970
3	#1 and #2	542
4	(#3) and (AB=Y PT=原著論文,会議録除く RD=ランダム化比較試験,準ランダム化比較試験 CK=ヒト)	2

Table S4 NICE critical appraisal for RCTs

Study question	**How is the question addressed in the study?**	**Kadowaki et al., 2022 [1]**	**Kumahara et al., 1985 [2]**
Was randomization carried out appropriately?	(yes/no/not clear/N/A)	Yes	Yes
Was the concealment of treatment allocation adequate?	(yes/no/not clear/N/A)	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	(yes/no/not clear/N/A)	Yes	No
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	(yes/no/not clear/N/A)	Yes	Yes
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	(yes/no/not clear/N/A)	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	(yes/no/not clear/N/A)	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	(yes/no/not clear/N/A)	Yes	Yes

NICE The National Institute for Health and Care Excellence, *RCT* randomized controlled trial
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

Table S5 CASP checklist for RCTs

Study question	**How is the question addressed in the study?**	**Kadowaki et al., 2022 [1]**	**Kumahara et al., 1985 [2]**
Did the study address a clearly focused research question?	(yes/no/can't tell)	Yes	Yes
Was the assignment of participants to interventions randomized?	(yes/no/can't tell)	Yes	Yes
Were all participants who entered the study accounted for at its conclusion?	(yes/no/can't tell)	Yes	No
Were the participants 'blind' to intervention they were given?	(yes/no/can't tell)	Yes	Yes
Were the study groups similar at the start of the randomized controlled trial?	(yes/no/can't tell)	Yes	No
Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?	(yes/no/can't tell)	Yes	Yes
Were the effects of intervention reported comprehensively?	(yes/no/can't tell)	Yes	No
Was the precision of the estimate of the intervention or treatment effect reported?	(yes/no/can't tell)	Yes	No
Do the benefits of the experimental intervention outweigh the harms and costs?	(yes/no/can't tell)	Can't tell	Can't tell
Can the results be applied to your local population/in your context?	(yes/no/can't tell)	Yes	Yes
Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?	(yes/no/can't tell)	Can't tell	Can't tell

CASP Critical Appraisal Skills Programme, *RCT* randomized controlled trial
Adapted from: CASP Randomised Controlled Trial Standard Checklist (2021)

Table S6 List of excluded studies

Author	Year	Title	Citation	Exclusion reason
Shi Q et al.	2022	Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials	Lancet. 2022; 399(10321):259-269	Study design
Wilding JPH et al.	2022	Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension	Diabetes, Obesity and Metabolism. 2022; 24(8):1553-1564	Geography
Inoue S et al.	1992	Clinical and basic aspects of an anorexiant, mazindol, as an antiobesity agent in Japan	American Journal of Clinical Nutrition. 1992;55(1 SUPPL.):199S-202S	Study design

Table S7 List of included studies

Author	Year	Title	Citation	Country
Kadowaki et al. [1]	2022	Semaglutide once a week in adults with overweight or obesity, with or without type 2 diabetes in an east Asian population (STEP 6): a randomised, double-blind, double-dummy, placebo-controlled, phase 3a trial	Lancet Diabetes and Endocrinology. 2022; 10(3):193-206	Japan, South Korea
Kumahara et al. [2]	1985	Clinical Evaluation of Mazindol, an Anorexiant, on Obesity - Multi-center Double-blind study in Comparison with Placebo (in Japanese)	Clinical Evaluation. 1985;13:461-515	Japan

Table S8 Baseline characteristics: age, BMI, sex, and SBP

Author, year, trial name/identifier	Intervention/ comparator	Dosage	Sample size, *n*	Age, mean (SD)	Age group, years, *n*		BMI, kg/m^2, mean (SD)	Female, *n* (%)	SBP, mmHg, mean (SD)
Kadowaki et al., 2022 [1], STEP 6/ NCT03811574	Semaglutide	2.4 mg once a week	199	52 (12.0)	NR		32.0 (4.60)	85 (43.0)	133 (14.0)
	Semaglutide	1.7 mg once a week	101	51 (10.0)	NR		31.60 (3.70)	37 (37.0)	135 (13.0)
	Placebo	N/A	101	50 (9.0)	NR		31.90 (4.20)	26 (26.0)	133 (14.0)
Kumahara et al., 1985 [2]	Mazindol	0.5 mg once daily for 2 weeks with increase in dose by 0.5 mg every 2 weeks thereafter, up to 3 mg at 12 weeks	114	NR	≤19	3	NR	83 (73.0)	NR
					20–29	13			
					30–39	17			
					40–49	29			
					50–59	35			
					60–69	13			
					>70	4			
	Placebo	N/A	114	NR	≤19	4	NR	89 (78.0)	NR
					20–29	8			
					30–39	19			
					40–49	29			
					50–59	37			
					60–69	16			
					>70	1			

BMI body mass index, *N/A* not applicable, *NR* not reported, *SBP* systolic blood pressure, *SD* standard deviation, *STEP* Semaglutide Treatment Effect in People with Obesity

Table S9 Baseline characteristics: lipid profile, prediabetes, T2D, and HbA_{1c}

Author, year, trial name/identifier	Intervention/ comparator	Dosage	Sample size, *n*	Lipid profile, mmol/L, geometric mean (CV)	Prediabetes, *n* (%)	T2D, *n* (%)	HbA_{1c}, %, mean (SD)
Kadowaki et al., 2022, [1] STEP 6/NCT03811574	Semaglutide	2.4 mg once a week	199	Total cholesterol: 5.10 (18.10); HDL cholesterol: 1.30 (23.60); triglyceride: 1.40 (47.30)	44 (22.0)	49 (25.0)	6.40 (1.20)
	Semaglutide	1.7 mg once a week	101	Total cholesterol: 5.30 (19.70); HDL cholesterol: 1.30 (24.10); triglyceride: 1.60 (57.80)	21 (21.0)	25 (25.0)	6.40 (1.10)
	Placebo	N/A	101	Total cholesterol: 5.30 (17.70); HDL cholesterol: 1.30 (22.0); triglyceride: 1.50 (52.80)	25 (25.0)	25 (25.0)	6.40 (1.10)

CV coefficient of variation percentage, *HbA_{1c}* glycated hemoglobin, *HDL* high-density lipoprotein, *N/A* not applicable, *SD* standard deviation, *STEP* Semaglutide Treatment Effect in People with Obesity, *T2D* type 2 diabetes

Table S10 Change in HbA_{1c}

Author, year, trial name/identifier	Intervention/ comparator	Dosage	Sample size, *n*	Timepoint	Change in HbA_{1c}, %, mean (SE)
Kadowaki et al., 2022, [1] STEP 6/ NCT03811574	Semaglutide	2.4 mg once a week	186	68 weeks	−0.96 (0.05); ETD (95% CI) vs placebo: −0.92 (−1.08, −0.77)
	Semaglutide	1.7 mg once a week	93	68 weeks	−0.93 (0.07); ETD (95% CI) vs placebo: −0.89 (−1.07, −0.71)
	Placebo	N/A	98	68 weeks	−0.03 (0.06)

CI confidence interval, *ETD* estimated treatment difference, *HbA_{1c}* glycated hemoglobin, *N/A* not applicable, *SE* standard error, *STEP* Semaglutide Treatment Effect in People with Obesity

Table S11 Proportion of patients not achieving early responder status

Author, year, trial name/identifier	Intervention/ comparator	Dosage	Timepoint	Sample size, *n*	Patients not achieving early responder status, *n* (%)
Kadowaki et al., 2022, [1] STEP 6/ NCT03811574	Semaglutide	2.4 mg once a week	68 weeks	193	33 (17.0)
	Semaglutide	1.7 mg once a week	68 weeks	98	27 (28.0)
	Placebo	N/A	68 weeks	100	79 (79.0)

Early responder status was defined as ≥ 5% weight loss from baseline

N/A not applicable, *STEP* Semaglutide Treatment Effect in People with Obesity

Table S12 Discontinuation in patients with obesity

Author, year, trial name/identifier	Intervention/ comparator	Dosage	Sample size, *n*	Timepoint	Overall discontinuation, *n* (%)	Reasons for discontinuation, *n* (%)
Kadowaki et al., 2022, [1] STEP 6/ NCT03811574	Semaglutide	2.4 mg once a week	199	68 weeks	13 (6.50)	AE: 5 (2.5) Protocol violation: 1 (0.5) At investigator's discretion: 1 (0.5) Withdrawal of consent: 3 (1.5) Other: 3 (1.5)
	Semaglutide	1.7 mg once a week	100	68 weeks	7 (7.0)	AE: 3 (3.0) Protocol violation: 1 (1.0) At investigator's discretion: 1 (1.0) Withdrawal of consent: 2 (2.0)
	Placebo	N/A	101	68 weeks	3 (3.0)	AE: 1 (1.0) Other: 2 (2.0)
Kumahara et al., 1985 [2]	Mazindol	0.5 mg once every 2 weeks and increasing by 0.5 mg every 2 weeks; dose escalated to 3 mg at 12 weeks	114	12 weeks	17 (14.90)	Non-responder's discontinuation: 1 (0.9) Other: 16 (14.6)
	Placebo	0.5 mg once every 2 weeks and increasing by 0.5 mg every 2 weeks; dose escalated to 3 mg at 12 weeks	114	12 weeks	16 (14.0)	Non-responder's discontinuation: 3 (2.6) Other: 13 (11.4)

AE adverse event, *N/A* not applicable, *STEP* Semaglutide Treatment Effect in People with Obesity

Table S13 Feasibility assessment: inconsistency between the clinical trial and the drug indication

	Kumahara et al., 1985 [2]	**Indication of mazindol [3]**
Population	Patients with simple or symptomatic obesity having ≥ 20% higher weight than the standard body weight	Patients with ≥ +70% of degree of obesity or BMI ≥ 35 kg/m^2
Use	12 weeks; 4-week observation period followed by 1 tablet per day during the first 2 weeks, then flexible increase of dose by addition of one tablet to daily dose every 2 weeks until week 12 (to a maximum of 6 tablets per day)	As short as possible, for a maximum of 12 weeks; usually 1 tablet per day, for a maximum of 3 tablets per day

BMI body mass index

Table S14 Naïve comparison: base case (using outcomes in STEP 6 at week 20)

Outcome	Mean change (SE) (+: improved; −: worsened)		Differential mean (SE)*		Difference (Sema – Mzd) (95% CI)
	STEP 6 [1] **at week 20**	**Kumahara 1985 [2]** **at week 12**	**Sema – Pla**	**Mzd – Pla**	
Body weight change, kg	Sema: 7.0 (0.3**) Pla: 2.1 (0.3**)	Mzd: 4.19 (0.42) Pla: 1.20 (0.24)	4.9 (0.4†,‡)	2.99 (0.48‡)	1.9 (0.7, 3.2)
SBP change, mmHg	Sema: 10 (1.0**) Pla: 5 (1.3**)	Mzd: 1.5† (2.7‡) Pla: 3.5† (2.6‡)	5.0 (1.6†,‡)	−2.0 (3.8‡)	7.0 (−1.0, 15.0)
Change of lipid levels	No data	**Total cholesterol:** • Mzd: 8.6 (6.4‡); Pla: 5.8 (7.1‡) **LDL cholesterol:** • Mzd: 77.2 (140.9‡); Pla: 52.1 (86.4‡) **HDL cholesterol:** • Mzd: 0.3 (2.1‡); Pla: −0.2 (2.2‡) **Triglycerides:** • Mzd: 20.1 (15.0‡); Pla: −5.0 (16.9‡)	No data	**Total cholesterol:** • 2.8 (9.6‡) **LDL cholesterol:** • 25.1 (165.3‡) **HDL cholesterol:** • 0.5 (3.1‡) **Triglycerides:** • 25.1 (22.6‡)	–

CI confidence interval, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *Mzd* mazindol, *Pla* placebo, *SBP* systolic blood pressure, *SD* standard deviation, *SE* standard error, *Sema* semaglutide, *sqrt* square root, *STEP* Semaglutide Treatment Effect in People with Obesity
*Differential mean: [mean change]Sema/Mzd – [mean change]Pla
**SE was calculated by # of patients (*n*) and SD (SD/sqrt(*n*))
†Difference of mean values reported in baseline and week 12
‡SE was calculated by $\text{sqrt}(SE_1^2 + SE_2^2)$

Table S15 Naïve comparison: scenario (using outcomes in STEP 6 at week 28)

Outcome	Mean change (SE) (+: improved; −: worsened)		Differential mean (SE)*		Difference (Sema – Mzd) (95% CI)
	STEP 6 [1] at week 28	**Kumahara 1985 [2] at week 12**	**Sema – Pla**	**Mzd – Pla**	
Body weight change, kg	Sema: 8.6 (0.4**) Pla: 2.3 (0.4**)	Mzd: 4.19 (0.42) Pla: 1.20 (0.24)	6.3 (0.5†,‡)	2.99 (0.48‡)	3.3 (1.9, 4.7)
SBP change, mmHg	Sema: 10 (1.0**) Pla: 4 (1.4**)	Mzd: 1.5† (2.7‡) Pla: 3.5† (2.6‡)	6.0 (1.7†,‡)	−2.0 (3.8‡)	8.0 (−0.1, 16.1)
Change of lipid levels	No data	**Total cholesterol:** • Mzd: 8.6 (6.4‡); Pla: 5.8 (7.1‡) **LDL cholesterol:** • Mzd: 77.2 (140.9‡); Pla: 52.1 (86.4‡) **HDL cholesterol:** • Mzd: 0.3 (2.1‡); Pla: −0.2 (2.2‡) **Triglycerides:** • Mzd: 20.1 (15.0‡); Pla: −5.0 (16.9‡)	No data	**Total cholesterol:** • 2.8 (9.6‡) **LDL cholesterol:** • 25.1 (165.3‡) **HDL cholesterol:** • 0.5 (3.1‡) **Triglycerides:** • 25.1 (22.6‡)	–

CI confidence interval, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *Mzd* mazindol, *Pla* placebo, *SBP* systolic blood pressure, *SD* standard deviation, *SE* standard error, *Sema* semaglutide, *sqrt* square root, *STEP* Semaglutide Treatment Effect in People with Obesity
*Differential mean: [mean change]Sema/Mzd – [mean change]Pla
**SE was calculated by # of patients (*n*) and SD (SD/sqrt(*n*))
†Difference of mean values reported in baseline and week 12
‡SE was calculated by sqrt($SE_1^2 + SE_2^2$)

References

1. Kadowaki T, Isendahl J, Khalid U, Lee SY, Nishida T, Ogawa W, et al. Semaglutide once a week in adults with overweight or obesity, with or without type 2 diabetes in an east Asian population (STEP 6): a randomised, double-blind, double-dummy, placebo-controlled, phase 3a trial. Lancet Diabetes Endocrinol. 2022;10(3):193–206.

2. Kumahara Y, Kumagai A, Goto Y, Shizume K, Naito C, Onishi T. Clinical evaluation of mazindol, an anorexiant, on obesity-multi-center double-blind study in comparison with placebo (Article in Japanese). Clin Eval. 1985;13:461–514.

3. Pharmaceuticals and Medical Devices Agency. Sanorex Tablets 0.5 mg (Article in Japanese). 2022. https://www.info.pmda.go.jp/go/pack/1190008F1020_4_03/ Accessed 1 Jul 2023.