

INTRODUCTION

- Prevalence of **pediatric obesity** is approaching **1 in 5** children and adolescents aged 2-19 years in the US.
- For these children, and particularly those with severe obesity, pediatricians have a paucity of safe, effective and durable weight-reducing pharmaceutical interventions with high-grade evidence.
- While GLP-1 receptor agonists have proven to be effective in reducing weight and improving glucose control **in adults**, their effects in children and adolescents with obesity is less clear.

AIM

This meta-analysis study aimed to determine the:

- . Weight effects
- 2. BMI/BMI z-score effects
- 3. Cardiometabolic effects
- 4. Gastrointestinal side-effects

of GLP-1 receptor agonists in children with obesity.

METHOD

Databases & Searching

Web of Science, PubMed/MEDLINE, and Scopus databases were searched from 01/01/1994-01/01/2021 for randomized control trials examining the weight, BMI, cardiometabolic or gastrointestinal effects of GLP-1 receptor agonists in children and adolescents with obesity.

Data Abstraction

Data were extracted by two independent surveyors and a random effects model was applied to meta-analyze generic inverse variance outcomes.

Primary Outcomes

Related to weight and cardiometabolic profile, while secondary outcomes of interest were gastrointestinalrelated treatment-emergent adverse events.

- 0%).

- . Were effective in modestly reducing weight
- 2. Improved glycaemic control
- 4. Are well tolerated despite increased nausea
- 5. Do not commonly cause pancreatitis or MTC

EFFICACY AND TOLERABILITY OF GLP-1 RECEPTOR AGONISTS IN CHILDREN AND ADOLESCENTS WITH OBESITY: A META-ANALYSIS

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RESULTS

• 9 studies with 574 participants were identified, of which 3 involved exenatide and 6 involved liraglutide.

Figure 1 GLP-1 receptor agonists use caused a modest reduction in body weight (mean difference [MD] -1.50 [-2.50,-0.50] kg, l² 64%), BMI (MD -1.24 [-1.71,-0.77] kg/m², l² 0%), and BMI zscore (MD -0.14 [-0.23,-0.06], l² 43%).

Figure 2 Glycemic control was improved in children with proven insulin resistance (HbA1c MD -1.05 [-1.93,-0.18] %, I² 76%).

Figure 3 Although no lipid profile *improvements were noted, a modest* decrease in systolic blood pressure was detected (MD -2.30 [-4.11,-0.49] mmHg; I²

Finally, analysis of gastrointestinal-related treatment-emergent adverse events revealed an increased risk of nausea (risk ratio 2.11 [1.44,3.09]; I² 0%), without significant increases in other gastrointestinal symptoms.

			Mean Difference
Mean Difference	SE	Weight	
-3.9	1.6378	7.1%	-3.90 [-7.11, -0.69
-3	1.4796	8.2%	-3.00 [-5.90, -0.10
-0.2707	0.4305	22.2%	-0.27 [-1.11, 0.57
		37.5%	-2.02 [-4.54, 0.49
= 3.50; Chi ² = 7.23,	df = 2 (F	P = 0.03);	$I^2 = 72\%$
: Z = 1.58 (P = 0.11	.)		
-4.5	1.3623	9.2%	-4.50 [-7.17, -1.83
-1.5	1.0408	12.6%	-1.50 [-3.54, 0.54
-1.31	0.6174	19.1%	-1.31 [-2.52, -0.10
-0.3184	0.4661	21.7%	-0.32 [-1.23, 0.60
		62.5%	-1.51 [-2.85, -0.17
= 1.17; Chi ² = 9.22,	df = 3 (F	P = 0.03);	$I^2 = 67\%$
Z = 2.21 (P = 0.03)	;)		
		100.0%	-1.50 [-2.50, -0.50
= 0.98; Chi ² = 16.83	L, df = 6	(P = 0.01)); $I^2 = 64\%$
		-	
ferences: $Chi^2 = 0.1$	3, $df = 1$	(P = 0.7)	2), $I^2 = 0\%$
	-3.9 -3 -0.2707 = 3.50; Chi ² = 7.23, : Z = 1.58 (P = 0.11) -4.5 -1.5 -1.31 -0.3184 = 1.17; Chi ² = 9.22, : Z = 2.21 (P = 0.03) = 0.98; Chi ² = 16.81 : Z = 2.95 (P = 0.00)	$-3.9 1.6378 \\ -3 1.4796 \\ -0.2707 0.4305 \\ = 3.50; Chi^{2} = 7.23, df = 2 (F) \\ : Z = 1.58 (P = 0.11) \\ -4.5 1.3623 \\ -1.5 1.0408 \\ -1.31 0.6174 \\ -0.3184 0.4661 \\ = 1.17; Chi^{2} = 9.22, df = 3 (F) \\ : Z = 2.21 (P = 0.03) \\ = 0.98; Chi^{2} = 16.81, df = 6 \\ : Z = 2.95 (P = 0.003) \\ \end{array}$	$\begin{array}{r} -3.9 \ 1.6378 \ 7.1\% \\ -3 \ 1.4796 \ 8.2\% \\ -0.2707 \ 0.4305 \ 22.2\% \\ \mathbf{37.5\%} \\ = 3.50; \ Chi^2 = 7.23, \ df = 2 \ (P = 0.03); \\ : \ Z = 1.58 \ (P = 0.11) \\ \end{array}$ $\begin{array}{r} -4.5 \ 1.3623 \ 9.2\% \\ -1.5 \ 1.0408 \ 12.6\% \\ -1.31 \ 0.6174 \ 19.1\% \\ -0.3184 \ 0.4661 \ 21.7\% \\ \mathbf{62.5\%} \\ = 1.17; \ Chi^2 = 9.22, \ df = 3 \ (P = 0.03); \\ : \ Z = 2.21 \ (P = 0.03) \\ \end{array}$

В вмі Mean Difference Study or Subgroup 1.2.1 Exenatide SE Weight IV, Random, 95% CI 12.9% -1.71 [-3.01, -0.41] 1.13 0.4592 27.0% -1.13 [-2.03, -0.23] -0.83 0.4337 30.3% -0.83 [-1.68, 0.02] 70.2% -1.11 [-1.67, -0.55] Heterogeneity: Tau² = 0.00; Chi² = 1.24, df = 2 (P = 0.54); I² = 0% Test for overall effect: Z = 3.89 (P = 0.000)-1.2 1.6219 2.2% -1.20 [-4.38, 1.98] 29.8% -1.55 [-2.41, -0.70] Zhou 2017 Subtotal (95% CI) Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0\%$ Test for overall effect: Z = 3.55 (P = 0.0004) Total (95% CI) 100.0% -1.24 [-1.71, -0.77] Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.01$, df = 4 (P = 0.73); $I^2 = 0\%$ Test for overall effect: Z = 5.20 (P < 0.00001) Test for subgroup differences: $Chi^2 = 0.73$, df = 1 (P = 0.39), $I^2 = 0\%$

Study or Subarous	Mean Difference	C E	Waight	Mean Difference
Study or Subgroup 1.3.1 Exenatide	Mean Difference	3E	Weight	IV, Random, 95%
Weghuber 2020	-0.09	0.0459	30.5%	-0.09 [-0.18, -0.0
Subtotal (95% CI)			30.5%	-0.09 [-0.18, -0.00
Heterogeneity: Not ap	plicable			
Test for overall effect	•	5)		
1.3.2 Liraglutide				
Mastrandrea 2019	-0.28	0.0969	13.6%	-0.28 [-0.47, -0.0
Kelly 2020	-0.22	0.0765	18.6%	-0.22 [-0.37, -0.0
Tamborlane 2019	-0.18	0.0765	18.6%	-0.18 [-0.33, -0.0
Danne 2017	-0.02	0.0765	18.6%	-0.02 [-0.17, 0.1
Subtotal (95% CI)			69.5%	-0.17 [-0.28, -0.00
Heterogeneity: Tau ² =	= 0.01; Chi ² = 5.56,	df = 3 (I	P = 0.14);	$l^2 = 46\%$
Test for overall effect	Z = 3.06 (P = 0.00))2)		
Total (95% CI)			100.0%	-0.14 [-0.23, -0.00
Heterogeneity: Tau ² =	= 0.00: Chi ² = 7.03.	df = 4 (I)	P = 0.13	$l^2 = 43\%$
Test for overall effect				
Test for subgroup dif			(P - 0.2)	7) $I^2 = 16.4\%$

Figure 1 | Forrest Plot of Mean Difference Change in Weight BMI, and BMI z-score Following GLP-1 Receptor Agonist Intervention in Children with Obesity. Studies are subgrouped by the specific intervention. BMI, body mass

CONCLUSIONS

• The two GLP-1RAs uncovered in the paediatric obesity literature were exenatide and liraglutide.

In children and adolescents with obesity, GLP-1RAs:

3. Reduced systolic blood pressure

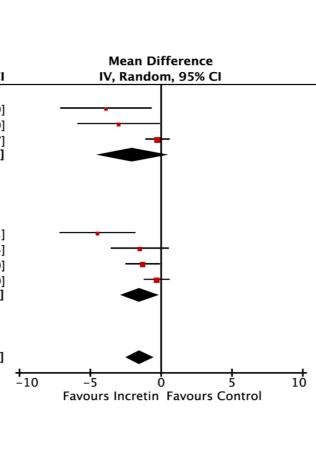
• This SRMA is limited by the fact that roughly half of the synthesised data arose from a single RCT.

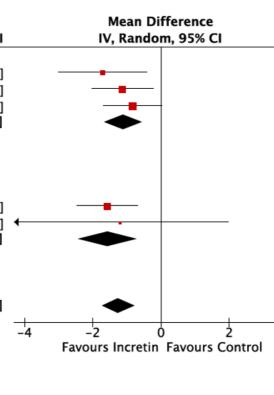
Pediatr. 2017;181:146-53 e3.

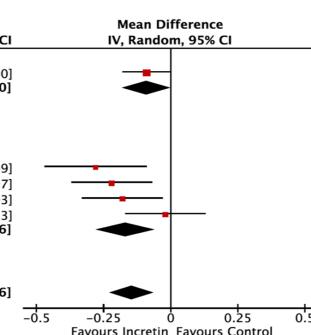
medicine. 2019;381:637-46.

Obes. 2019;14:e12495.

medicine. 2020;382:2117-28.







2.1.1 Insulin Resistant		<u> </u>	IV, Random, 95% CI	IV, Random, 95% CI
Klein 2014	-2.1435 0.590	2.6%	-2.14 [-3.30, -0.99]	←
Tamborlane 2019	-1.06 0.30	1 8.1%	-1.06 [-1.65, -0.47]	
Zhou 2017	-0.3006 0.310	5 7.7%	-0.30 [-0.91, 0.31]	
Subtotal (95% CI)		18.4%	-1.05 [-1.93, -0.18]	
Heterogeneity: $Tau^2 = 0.4$	4; $Chi^2 = 8.41$, $df = 2$	P = 0.01	; $I^2 = 76\%$	
Test for overall effect: Z =				
2.1.2 Mixed Population				
Danne 2017	-0.12 0.096	9 24.0%	-0.12 [-0.31, 0.07]	- +
Kelly 2013	-0.11 0.061	2 27.8%	-0.11 [-0.23, 0.01]	-
Kelly 2020	-0.06 0.035			-
Subtotal (95% CI)			-0.08 [-0.13, -0.02]	•
Heterogeneity: $Tau^2 = 0.0$	0; $Chi^2 = 0.71$, $df = 2$	P = 0.70	$I^2 = 0\%$	
Test for overall effect: Z =		. ,		
Total (95% CI)		100.0%	-0.24 [-0.44, -0.05]	•
Heterogeneity: $Tau^2 = 0.0$	3; Chi ² = 23.83, df =	5 (P = 0.00)	$(002); I^2 = 79\%$	
Test for overall effect: Z =				-2 -1 0 1 Favours Incretin Favours Contro
Test for subgroup differer	ces: $Chi^2 = 4.73$. df =	= 1 (P = 0.0)	(3), $l^2 = 78.9\%$	Favours incretin Favours contro
			Mean Difference	Mean Difference
Ctudy or Cubaroup Maa	n Difforence C	E Waight	IV Bandom OF% CI	
	n Difference S	E Weight	IV, Random, 95% CI	IV, Random, 95% Cl
2.2.1 Insulin Resistant				IV, Random, 95% CI
2.2.1 Insulin Resistant Tamborlane 2019	-32.6 12.500	2 0.6%	-32.60 [-57.10, -8.10]	IV, Random, 95% CI
2.2.1 Insulin Resistant Tamborlane 2019 Klein 2014	-32.6 12.500 -25.9 19.964	2 0.6% 7 0.2%	-32.60 [-57.10, -8.10] -25.90 [-65.03, 13.23]	IV, Random, 95% CI
2.2.1 Insulin Resistant Tamborlane 2019 Klein 2014 Zhou 2017	-32.6 12.500	2 0.6% 7 0.2% 2 38.0%	-32.60 [-57.10, -8.10] -25.90 [-65.03, 13.23] -0.44 [-0.98, 0.10]	IV, Random, 95% CI
2.2.1 Insulin Resistant Tamborlane 2019 Klein 2014 Zhou 2017 Subtotal (95% CI)	-32.6 12.500 -25.9 19.964 -0.44 0.276	2 0.6% 7 0.2% 2 38.0% 38.8%	-32.60 [-57.10, -8.10] -25.90 [-65.03, 13.23] -0.44 [-0.98, 0.10] - 16.26 [-41.23, 8.71]	IV, Random, 95% CI
2.2.1 Insulin Resistant Tamborlane 2019 Klein 2014 Zhou 2017	-32.6 12.500 -25.9 19.964 -0.44 0.276 .40; Chi ² = 8.24, df =	2 0.6% 7 0.2% 2 38.0% 38.8%	-32.60 [-57.10, -8.10] -25.90 [-65.03, 13.23] -0.44 [-0.98, 0.10] - 16.26 [-41.23, 8.71]	IV, Random, 95% CI
2.2.1 Insulin Resistant Tamborlane 2019 Klein 2014 Zhou 2017 Subtotal (95% CI) Heterogeneity: Tau ² = 350	-32.6 12.500 -25.9 19.964 -0.44 0.276 .40; Chi ² = 8.24, df =	2 0.6% 7 0.2% 2 38.0% 38.8%	-32.60 [-57.10, -8.10] -25.90 [-65.03, 13.23] -0.44 [-0.98, 0.10] - 16.26 [-41.23, 8.71]	IV, Random, 95% CI
2.2.1 Insulin Resistant Tamborlane 2019 Klein 2014 Zhou 2017 Subtotal (95% CI) Heterogeneity: Tau ² = 350 Test for overall effect: Z = 2.2.2 Mixed Population Danne 2017	-32.6 12.500 -25.9 19.964 -0.44 0.276 .40; Chi ² = 8.24, df =	2 0.6% 7 0.2% 2 38.0% 38.8% 2 (P = 0.02	-32.60 [-57.10, -8.10] -25.90 [-65.03, 13.23] -0.44 [-0.98, 0.10] - 16.26 [-41.23, 8.71]	IV, Random, 95% CI
2.2.1 Insulin Resistant Tamborlane 2019 Klein 2014 Zhou 2017 Subtotal (95% CI) Heterogeneity: Tau ² = 350 Test for overall effect: Z = 2.2.2 Mixed Population	-32.6 12.500 -25.9 19.964 -0.44 0.276 .40; Chi ² = 8.24, df = 1.28 (P = 0.20)	2 0.6% 7 0.2% 2 38.0% 38.8% 2 (P = 0.02) 6 6.9%	-32.60 [-57.10, -8.10] -25.90 [-65.03, 13.23] -0.44 [-0.98, 0.10] - 16.26 [-41.23, 8.71]); I ² = 76%	IV, Random, 95% CI
2.2.1 Insulin Resistant Tamborlane 2019 Klein 2014 Zhou 2017 Subtotal (95% CI) Heterogeneity: Tau ² = 350 Test for overall effect: Z = 2.2.2 Mixed Population Danne 2017 Kelly 2013 Weghuber 2020	$\begin{array}{r} -32.6 & 12.500 \\ -25.9 & 19.964 \\ -0.44 & 0.276 \end{array}$ $\begin{array}{r} .40; \ Chi^2 = 8.24, \ df = \\ 1.28 \ (P = 0.20) \end{array}$ $\begin{array}{r} -4.14 & 3.29 \\ -3.33 & 3.255 \\ -2 & 2.142 \end{array}$	2 0.6% 7 0.2% 2 38.0% 38.8% 2 (P = 0.02 6 6.9% 2 7.1% 9 13.2%	$-32.60 [-57.10, -8.10]$ $-25.90 [-65.03, 13.23]$ $-0.44 [-0.98, 0.10]$ $-16.26 [-41.23, 8.71]$); $I^2 = 76\%$ $-4.14 [-10.60, 2.32]$ $-3.33 [-9.71, 3.05]$ $-2.00 [-6.20, 2.20]$	IV, Random, 95% CI
2.2.1 Insulin Resistant Tamborlane 2019 Klein 2014 Zhou 2017 Subtotal (95% Cl) Heterogeneity: Tau ² = 350 Test for overall effect: Z = 2.2.2 Mixed Population Danne 2017 Kelly 2013 Weghuber 2020 Kelly 2020	$-32.6 12.500 \\ -25.9 19.964 \\ -0.44 0.276 \\ .40; Chi2 = 8.24, df = \\ 1.28 (P = 0.20) \\ -4.14 3.29 \\ -3.33 3.255 \\ -2 2.142 \\ -1.82 1.183 \\ $	2 0.6% 7 0.2% 2 38.0% 38.8% 2 (P = 0.02 6 6.9% 2 7.1% 9 13.2% 7 24.5%	$-32.60 [-57.10, -8.10]$ $-25.90 [-65.03, 13.23]$ $-0.44 [-0.98, 0.10]$ $-16.26 [-41.23, 8.71]$ $); ^{2} = 76\%$ $-4.14 [-10.60, 2.32]$ $-3.33 [-9.71, 3.05]$ $-2.00 [-6.20, 2.20]$ $-1.82 [-4.14, 0.50]$	IV, Random, 95% CI
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2.2.1 Insulin Resistant Tamborlane 2019 Klein 2014 Zhou 2017 Subtotal (95% CI) Heterogeneity: Tau ² = 350 Test for overall effect: Z = 2.2.2 Mixed Population Danne 2017 Kelly 2013 Weghuber 2020 Kelly 2020 Kelly 2020 Kelly 2012 Subtotal (95% CI) Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = Total (95% CI) Heterogeneity: Tau ² = 2.33	$-32.6 12.500$ $-25.9 19.964$ $-0.44 0.276$ $.40; Chi^{2} = 8.24, df = 1.28 (P = 0.20)$ $-4.14 3.29$ $-3.33 3.255$ $-2 2.142$ $-1.82 1.183$ $1.68 2.719$ $0; Chi^{2} = 2.37, df = 4 (1.97 (P = 0.05))$	2 0.6% 7 0.2% 2 38.0% 38.8% 2 (P = 0.02) 6 6.9% 2 7.1% 9 13.2% 7 24.5% 4 9.4% 61.2% P = 0.67); I 100.0%	$-32.60 [-57.10, -8.10]$ $-25.90 [-65.03, 13.23]$ $-0.44 [-0.98, 0.10]$ $-16.26 [-41.23, 8.71]$ $); ^{2} = 76\%$ $-4.14 [-10.60, 2.32]$ $-3.33 [-9.71, 3.05]$ $-2.00 [-6.20, 2.20]$ $-1.82 [-4.14, 0.50]$ $1.68 [-3.65, 7.01]$ $-1.76 [-3.51, -0.01]$ $^{2} = 0\%$ $-1.49 [-3.37, 0.39]$	IV, Random, 95% CI
2.2.1 Insulin Resistant Tamborlane 2019 Klein 2014 Zhou 2017 Subtotal (95% Cl) Heterogeneity: Tau ² = 350 Test for overall effect: Z = 2.2.2 Mixed Population Danne 2017 Kelly 2013 Weghuber 2020 Kelly 2020 Kelly 2020 Kelly 2012 Subtotal (95% Cl) Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = Total (95% Cl)	$-32.6 12.500$ $-25.9 19.964$ $-0.44 0.276$ $.40; Chi^{2} = 8.24, df = 1.28 (P = 0.20)$ $-4.14 3.29$ $-3.33 3.255$ $-2 2.142$ $-1.82 1.183$ $1.68 2.719$ $0; Chi^{2} = 2.37, df = 4 (1.97 (P = 0.05))$ $3; Chi^{2} = 12.53, df = 7$ $1.56 (P = 0.12)$	2 0.6% 7 0.2% 2 38.0% 38.8% 2 ($P = 0.02$ 6 6.9% 2 7.1% 9 13.2% 7 24.5% 4 9.4% 61.2% P = 0.67); I 100.0% ($P = 0.08$);	$-32.60 [-57.10, -8.10]$ $-25.90 [-65.03, 13.23]$ $-0.44 [-0.98, 0.10]$ $-16.26 [-41.23, 8.71]$ b; $ ^2 = 76\%$ $-4.14 [-10.60, 2.32]$ $-3.33 [-9.71, 3.05]$ $-2.00 [-6.20, 2.20]$ $-1.82 [-4.14, 0.50]$ $1.68 [-3.65, 7.01]$ $-1.76 [-3.51, -0.01]$ $^2 = 0\%$ $-1.49 [-3.37, 0.39]$ $ ^2 = 44\%$	IV, Random, 95% CI

Figure 2 | Forrest Plot of Mean Difference Change in Glycemic Control Following GLP-1 Receptor Agonist Intervention in Children with Obesity. Studies are subgrouped according to their exclusive inclusion of children and adolescents with some degree of insulin resistance (i.e., type-2 diabetes or prediabetes) or not (i.e., mixed population). HbA1c, glycated hemoglobin; FPG, fasting plasma glucose.

INCLUDED RCTS

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A HbA1c

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Kelly 2 Kelly 2 Total (Hetero Test fo	2012 (95% Cl) ogeneity: Chi ² =	-11.6 1.98 10.7 = 4.95, df = 3 (P = 0.			IV, Fixed, 95% CI -13.30 [-67.95, 41.35]	
Hetero Test fo	geneity: Chi ² =	= 4.95, df = 3 (P = 0.	5.1532 5.847 11.541	49.7% 38.6% 9.9%	-11.60 [-21.70, -1.50] 1.98 [-9.48, 13.44] 10.70 [-11.92, 33.32]	
וח ו		t: Z = 1.15 (P = 0.25)		100.0% 39%	-4.17 [-11.29, 2.95]	-200 -100 0 100 200 Favours Incretin Favours Control
Study	L-C or Subgroup	Mean Difference		Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% Cl
Zhou 2		-6.96	3.5205 9.2821	9.5%	-7.30 [-14.20, -0.40] -6.96 [-25.15, 11.23]	
Kelly 2 Kelly 2		1.52 6.93	7.3114 9.541	15.3% 9.0%	1.52 [-12.81, 15.85] 6.93 [-11.77, 25.63]	
Hetero		= 0.00; Chi ² = 2.81, t: Z = 1.62 (P = 0.11	df = 3 (P		-4.63 [-10.25, 0.98] ² = 0%	-20 -10 0 10 20 Favours Incretin Favours Control
	J lyceride	PS Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% Cl
Kelly 2 Zhou 2	012	-12.57			-12.57 [-59.41, 34.27] -5.31 [-25.67, 15.05]	
Kelly 2	2017	-5.31				
•		-4.71	20.6279 8.2655	8.4% 52.3%	-4.71 [-45.14, 35.72] 8.00 [-8.20, 24.20]	
Weghu Total (Hetero	013 ber 2020 (95% CI) geneity: Tau ² =	-4.71 8 = 0.00; Chi ² = 1.48,	8.2655 df = 3 (P =	52.3% 100.0%	8.00 [-8.20, 24.20] 1.24 [-10.47, 12.96]	
Weghu Total (Hetero Test fo	013 ber 2020 (95% CI) geneity: Tau ² = or overall effect	-4.71 8 = 0.00; Chi ² = 1.48, t: Z = 0.21 (P = 0.84)	8.2655 df = 3 (P =	52.3% 100.0% = 0.69); l ²	8.00 [-8.20, 24.20] 1.24 [-10.47, 12.96] ² = 0% Mean Difference	Favours Incretin Favours Control Mean Difference
Weghu Total (Hetero Test fo SBF Study Kelly 2	013 ber 2020 (95% CI) geneity: Tau ² = or overall effect or <u>Subgroup</u> 013	-4.71 8 = 0.00; Chi ² = 1.48, t: Z = 0.21 (P = 0.84) <u>Mean Difference</u> -6.36	8.2655 df = 3 (P = <u>SE</u> 3.6225	52.3% 100.0% = 0.69); l ² <u>Weight</u> 6.5%	8.00 [-8.20, 24.20] 1.24 [-10.47, 12.96] ² = 0% Mean Difference IV, Random, 95% CI -6.36 [-13.46, 0.74]	Favours Incretin Favours Control
Weghu Total (Hetero Test fo SBF Study Kelly 2 Kelly 2 Tambo	013 ber 2020 (95% CI) geneity: Tau ² = or overall effect or overall effect 013 012 orlane 2019	-4.71 8 = 0.00; Chi ² = 1.48, f t: Z = 0.21 (P = 0.84) Mean Difference -6.36 -5.31 -2.07	8.2655 df = 3 (P = <u>SE</u> 3.6225 4.8878 1.7398	52.3% 100.0% = 0.69); l ² <u>Weight</u> 6.5% 3.6% 28.2%	8.00 [-8.20, 24.20] 1.24 [-10.47, 12.96] ² = 0% Mean Difference IV, Random, 95% CI -6.36 [-13.46, 0.74] -5.31 [-14.89, 4.27] -2.07 [-5.48, 1.34]	Favours Incretin Favours Control Mean Difference
Weghu Total (Hetero Test fo SBB Study Kelly 2 Kelly 2 Tambo Kelly 2	013 ber 2020 (95% CI) geneity: Tau ² = or overall effect or overall effect 013 012 orlane 2019	-4.71 8 = 0.00; Chi ² = 1.48, 4 t: Z = 0.21 (P = 0.84) <u>Mean Difference</u> -6.36 -5.31 -2.07 -2.05	8.2655 df = 3 (P = <u>SE</u> 3.6225 4.8878	52.3% 100.0% = 0.69); l ² <u>Weight</u> 6.5% 3.6%	8.00 [-8.20, 24.20] 1.24 [-10.47, 12.96] ² = 0% Mean Difference IV, Random, 95% CI -6.36 [-13.46, 0.74] -5.31 [-14.89, 4.27] -2.07 [-5.48, 1.34] -2.05 [-4.53, 0.43]	Favours Incretin Favours Control Mean Difference
Weghu Total (Hetero Test fo SBBF Study Kelly 2 Kelly 2 Tambo Kelly 2 Weghu Total (013 ber 2020 (95% CI) geneity: Tau ² = or overall effect or Subgroup 013 012 orlane 2019 020 ber 2020 (95% CI)	-4.71 8 = 0.00; Chi ² = 1.48, for the second state of the seco	8.2655 df = 3 (P = 3.6225 4.8878 1.7398 1.2653 3.2143	52.3% 100.0% = 0.69); 1 ² 6.5% 3.6% 28.2% 53.4% 8.3% 100.0%	8.00 [-8.20, 24.20] 1.24 [-10.47, 12.96] ² = 0% Mean Difference IV, Random, 95% Cl -6.36 [-13.46, 0.74] -5.31 [-14.89, 4.27] -2.07 [-5.48, 1.34] -2.05 [-4.53, 0.43] -0.20 [-6.50, 6.10] -2.30 [-4.11, -0.49]	Favours Incretin Favours Control
Weghu Total (Hetero Test fo SBF Study Kelly 2 Kelly 2 Kelly 2 Tambo Kelly 2 Weghu Total (Hetero	013 ber 2020 (95% CI) geneity: Tau ² = or overall effect or subgroup 013 012 orlane 2019 020 ber 2020 (95% CI) ogeneity: Tau ²	-4.71 8 = 0.00; Chi ² = 1.48, 4 t: Z = 0.21 (P = 0.84) <u>Mean Difference</u> -6.36 -5.31 -2.07 -2.05	8.2655 df = 3 (P = 3.6225 4.8878 1.7398 1.2653 3.2143 , df = 4 (P	52.3% 100.0% = 0.69); 1 ² 6.5% 3.6% 28.2% 53.4% 8.3% 100.0%	8.00 [-8.20, 24.20] 1.24 [-10.47, 12.96] ² = 0% Mean Difference IV, Random, 95% Cl -6.36 [-13.46, 0.74] -5.31 [-14.89, 4.27] -2.07 [-5.48, 1.34] -2.05 [-4.53, 0.43] -0.20 [-6.50, 6.10] -2.30 [-4.11, -0.49]	Favours Incretin Favours Control Mean Difference
Weghu Total (Hetero Test fo SBF Study Kelly 2 Kelly 2 Kelly 2 Tambo Kelly 2 Weghu Total (Hetero Test fo	013 ber 2020 (95% CI) geneity: Tau ² = or overall effect or subgroup 013 012 orlane 2019 020 ber 2020 (95% CI) ogeneity: Tau ² or overall effect	-4.71 8 $= 0.00; Chi^{2} = 1.48, f$ $t: Z = 0.21 (P = 0.84)$ $\frac{Mean Difference}{-6.36}$ -5.31 -2.07 -2.05 -0.2 $= 0.00; Chi^{2} = 2.12$ $t: Z = 2.49 (P = 0.02)$	8.2655 df = 3 (P = 3.6225 4.8878 1.7398 1.2653 3.2143 , df = 4 (P 1)	52.3% 100.0% = 0.69); 1 ² Weight 6.5% 3.6% 28.2% 53.4% 8.3% 100.0% P = 0.71);	8.00 [-8.20, 24.20] 1.24 [-10.47, 12.96] $^2 = 0\%$ Mean Difference IV, Random, 95% Cl -6.36 [-13.46, 0.74] -5.31 [-14.89, 4.27] -2.07 [-5.48, 1.34] -2.05 [-4.53, 0.43] -0.20 [-6.50, 6.10] -2.30 [-4.11, -0.49] ; $l^2 = 0\%$ Mean Difference	Favours Incretin Favours Control Mean Difference IV, Random, 95% CI
Weghu Total (Hetero Test fo SBF Study Kelly 2 Kelly 2 Weghu Total (Hetero Test fo DBF Study 0 Kelly 2	013 ber 2020 (95% CI) geneity: Tau ² = or overall effect or subgroup 013 012 orlane 2019 020 ber 2020 (95% CI) geneity: Tau ² or overall effect or overall effect	-4.71 8 $= 0.00; Chi^{2} = 1.48, finite interval inter$	8.2655 df = 3 (P = 3.6225 4.8878 1.7398 1.2653 3.2143 , df = 4 (P L) <u>SE</u> 7.8216	52.3% 100.0% = 0.69); 1 ² <u>Weight</u> 6.5% 3.6% 28.2% 53.4% 8.3% 100.0% 2 = 0.71); <u>Weight</u> 1.2%	8.00 [-8.20, 24.20] 1.24 [-10.47, 12.96] $^2 = 0\%$ Mean Difference IV, Random, 95% CI -6.36 [-13.46, 0.74] -5.31 [-14.89, 4.27] -2.07 [-5.48, 1.34] -2.05 [-4.53, 0.43] -0.20 [-6.50, 6.10] -2.30 [-4.11, -0.49] ; $ ^2 = 0\%$ Mean Difference IV, Random, 95% CI -3.00 [-18.33, 12.33]	Favours Incretin Favours Control
Weghu Total (Hetero Test fo SBF Study Kelly 2 Kelly 2 Kelly 2 Weghu Total (Hetero Test fo DBF Study 0 Kelly 2 Weghu Lettero Kelly 2 Kelly 2 Kel	013 ber 2020 (95% CI) geneity: Tau ² = or overall effect 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	-4.71 8 $= 0.00; Chi^{2} = 1.48, Finite interval inter$	8.2655 df = 3 (P = 3.6225 4.8878 1.7398 1.2653 3.2143 , df = 4 (P L) <u>SE</u> 7.8216 2.0409 1.4541	52.3% 100.0% = 0.69); 1 ² Weight 6.5% 3.6% 28.2% 53.4% 8.3% 100.0% P = 0.71); Weight 1.2% 15.4% 27.4%	8.00 [-8.20, 24.20] 1.24 [-10.47, 12.96] $^2 = 0\%$ Mean Difference IV, Random, 95% Cl -6.36 [-13.46, 0.74] -5.31 [-14.89, 4.27] -2.07 [-5.48, 1.34] -2.05 [-4.53, 0.43] -0.20 [-6.50, 6.10] -2.30 [-4.11, -0.49] ; $l^2 = 0\%$ Mean Difference IV, Random, 95% Cl -3.00 [-18.33, 12.33] -2.90 [-6.90, 1.10] -0.26 [-3.11, 2.59]	Favours Incretin Favours Control Mean Difference IV, Random, 95% CI
Weghu Total (Hetero Test fo SBF Study Kelly 2 Kelly 2 Kelly 2 Weghu Total (Hetero Test fo DBF Study 0 Kelly 2 Weghu	013 ber 2020 (95% CI) geneity: Tau ² = or overall effect 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	-4.71 8 $= 0.00; Chi^{2} = 1.48, 4$ $: Z = 0.21 (P = 0.84)$ $\frac{Mean Difference}{-6.36}$ -5.31 -2.07 -2.05 -0.2 $= 0.00; Chi^{2} = 2.12$ $: Z = 2.49 (P = 0.0)$ $\frac{Mean Difference}{-3}$ -2.9 -0.26 1.24	8.2655 df = 3 (P = 3.6225 4.8878 1.7398 1.2653 3.2143 , df = 4 (P L) <u>SE</u> 7.8216 2.0409	52.3% 100.0% = 0.69); 1 ² Weight 6.5% 3.6% 28.2% 53.4% 8.3% 100.0% P = 0.71); Weight 1.2% 15.4%	8.00 [-8.20, 24.20] 1.24 [-10.47, 12.96] $^2 = 0\%$ Mean Difference IV, Random, 95% CI -6.36 [-13.46, 0.74] -5.31 [-14.89, 4.27] -2.07 [-5.48, 1.34] -2.05 [-4.53, 0.43] -0.20 [-6.50, 6.10] -2.30 [-4.11, -0.49] ; $ ^2 = 0\%$ Mean Difference IV, Random, 95% CI -3.00 [-18.33, 12.33] -2.90 [-6.90, 1.10] -0.26 [-3.11, 2.59]	Favours Incretin Favours Control Mean Difference IV, Random, 95% CI

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