A novel approach to managing obesity in survivors of childhood brain tumors

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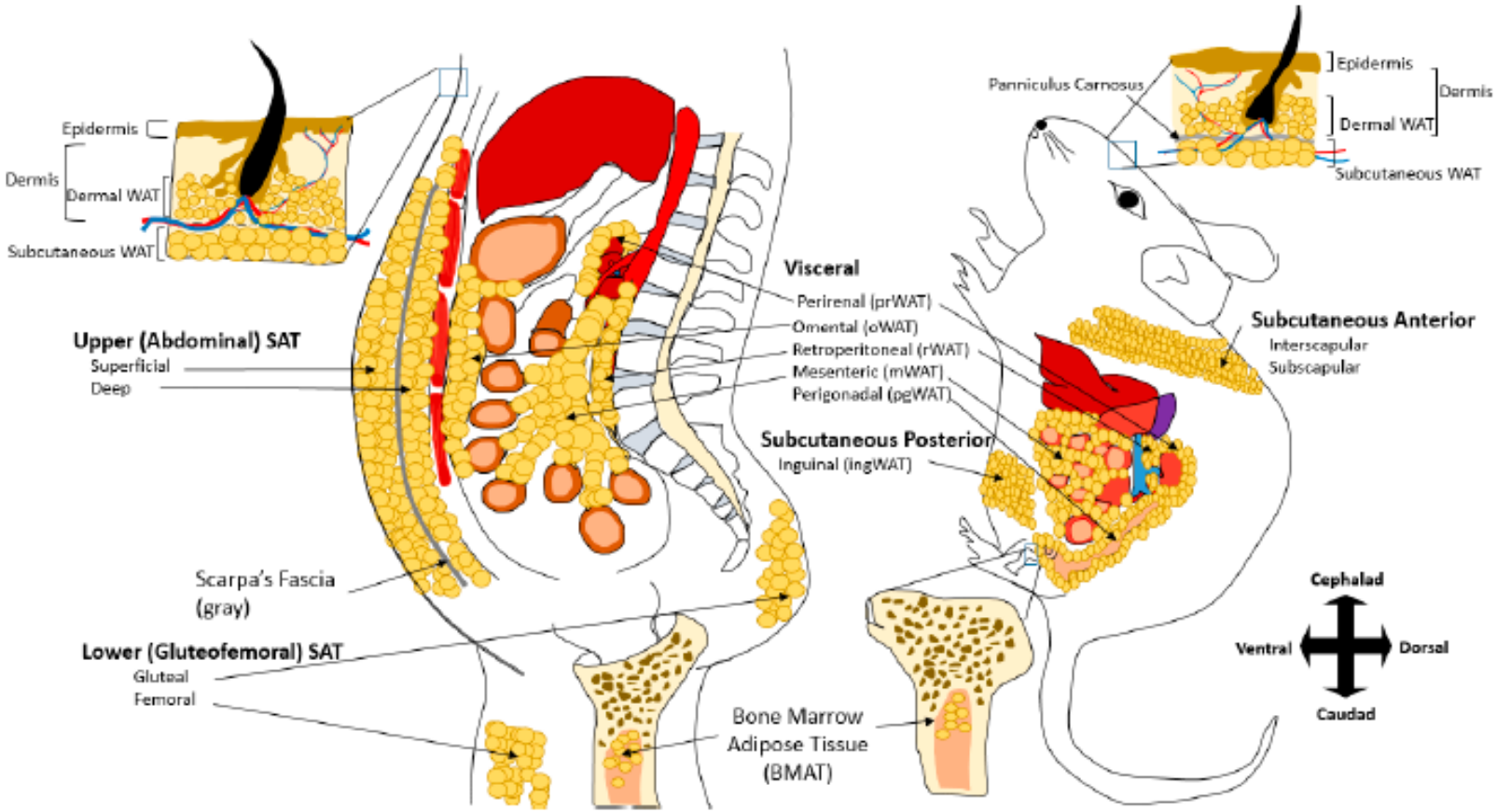
Objectives

1-Describe adiposity as a metabolic aftereffect in survivors of childhood brain tumors (SCBT)

2-Describe our journey to create a research program to assess the determinants of endometabolic risk in SCBT

3-Describe interventions to manage obesity in SCBT

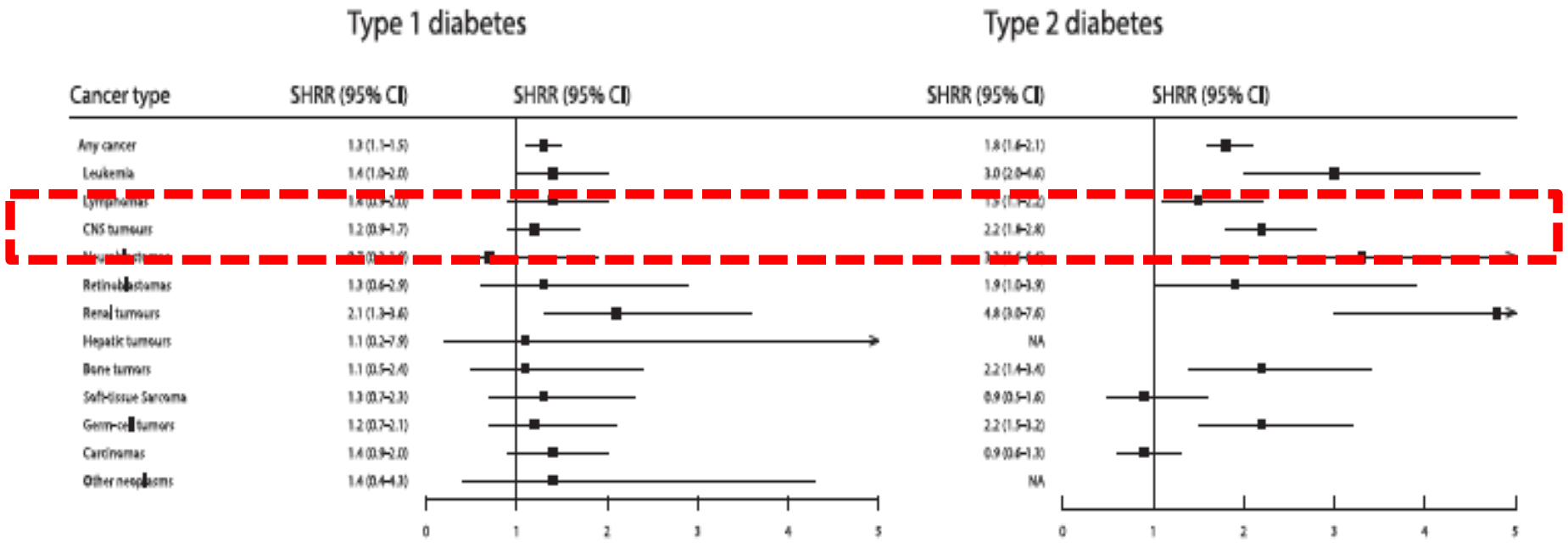
Not all adipose tissue depots are created equal



Luong Q et al. Biology **2019**, *8*(2), 23; https://doi.org/10.3390/biology8020023

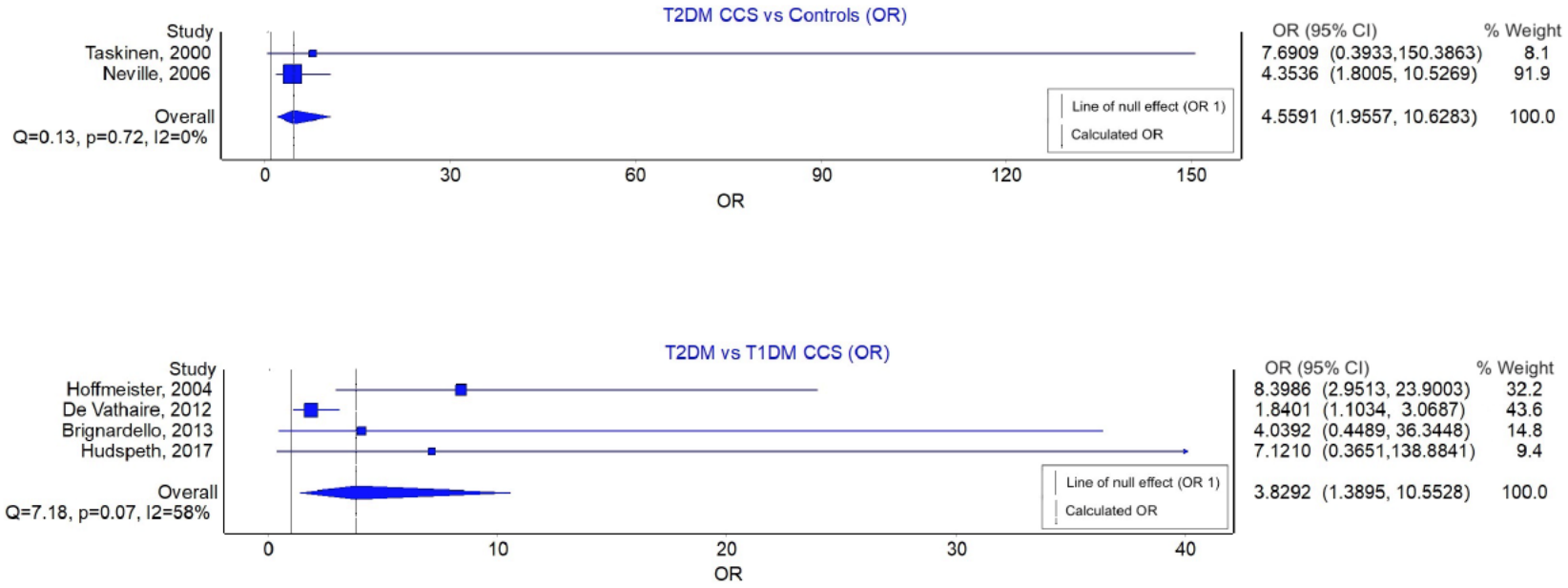
SCBT are at risk of developing type 2 diabetes

SCBT n=7913, median follow-up 10 years, 1-yr survival included



Holmqvist A S et al. Euro J cancer. 50, 1169-1175, 2014

SCBT are at risk of diabetes



Manuscript in preparation, 2024

As obesity is a global driver of cardiovascular disease and and type 2 diabetes: Questions

- Do SCBT have higher obesity rates than non-cancer controls?
- If SCBT do have obesity, why?
- Are there effective intervention to treat obesity now?

Open Access Research

BMJ Open

Recruitment feasibility to a cohort study of endocrine and metabolic health among survivors of childhood brain tumours: a report from the Canadian study of Determinants of Endometabolic Health in ChIlDrEn (CanDECIDE)

M Constantine Samaan,[1,2] Katrin Scheinemann,[1,3,4] Sarah Burrow,[5] Rejane F Dillenburg,[1,6] Ronald D Barr,[1,3] Kuan-Wen Wang,[1,2] Marlie Valencia,[1,2] Lehana Thabane[1,7,8,9,10]

Open Access Protocol

BMJ open accessible medical research

Canadian Study of Determinants of Endometabolic Health in ChIlDrEn (*CanDECIDE study*): a cohort study protocol examining the mechanisms of obesity in survivors of childhood brain tumours

M Constantine Samaan,[1,2] Lehana Thabane,[1,3,4,5,6] Sarah Burrow,[7] Rejane F Dillenburg,[1,8] Katrin Scheinemann[1,9]

CanDECIDE

Question

- Do SCBT have higher obesity rates than non-cancer controls?

clinical obesity

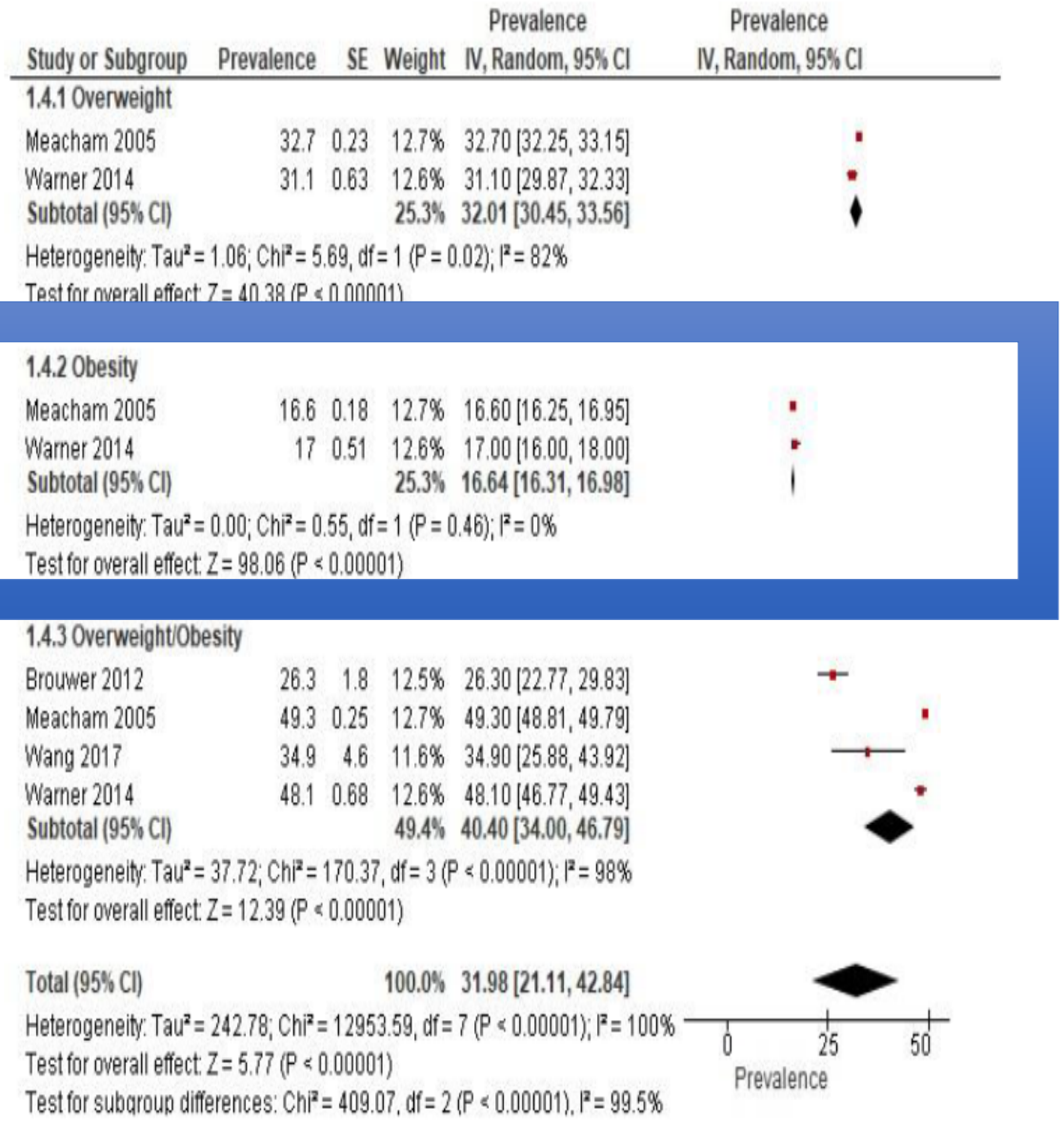
doi: 10.1111/cob.12224

Review

Overweight, obesity and adiposity in survivors of childhood brain tumours: a systematic review and meta-analysis

K-W. Wang[1,2,3], A. Fleming[1,3,4], D. L. Johnston[5], S. M. Zelcer[6], S. R. Rassekh[7], S. Ladhani[1,2], A. Socha[1,2], J. Shinuda[1,2], S. Jaber[1,2], S. Burrow[8], S. K. Singh[9,10], L. Banfield[11], R. J. de Souza[3,12], L. Thabane[3,12,13,14,15] and M. C. Samaan[1,2,3,12]

The prevalence of obesity in non-cancer controls

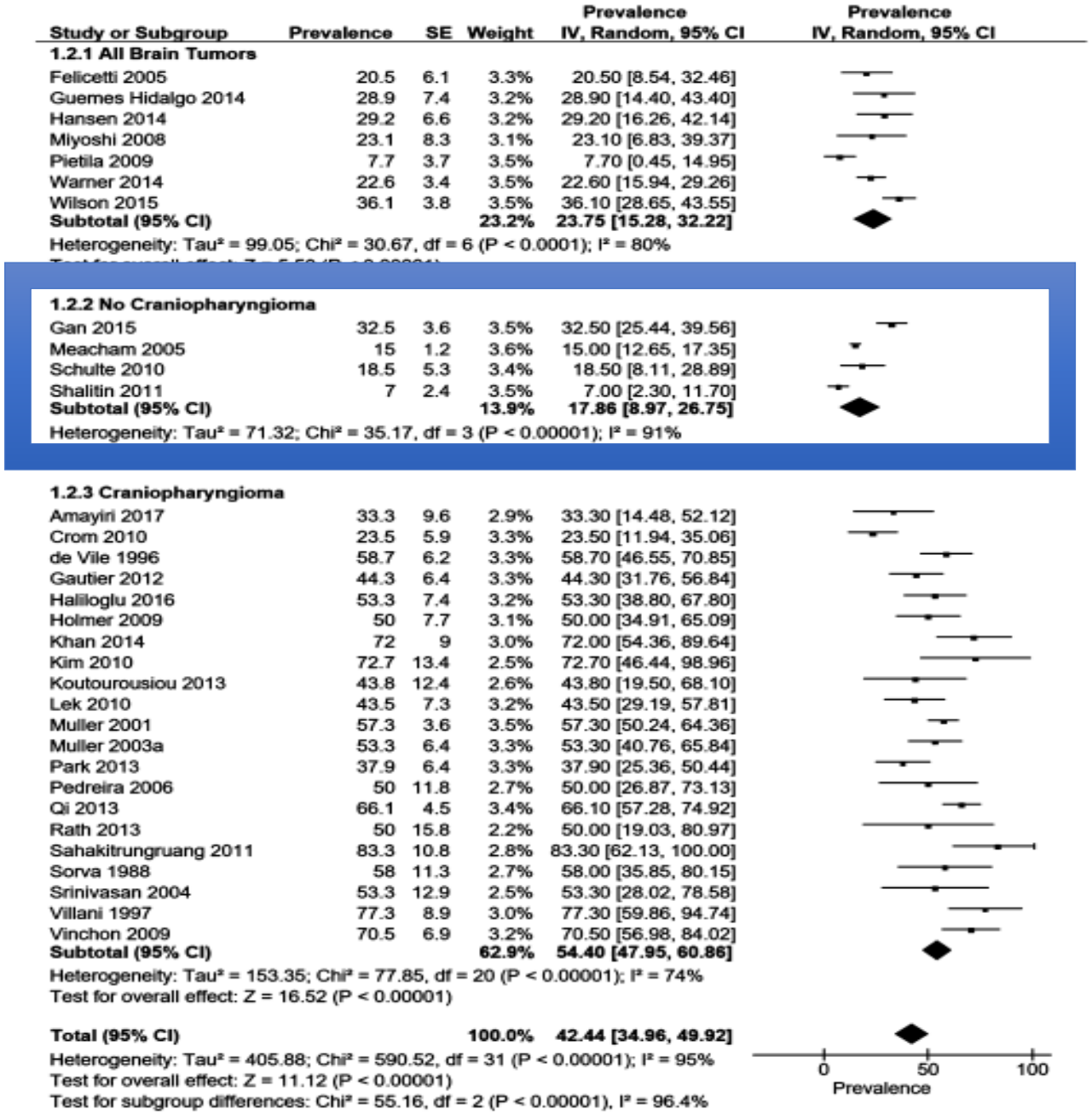


Wang KW et al. Clin Obes. 2018 Feb;8(1):55-67

The prevalence of obesity in SCBT

No CP

CP

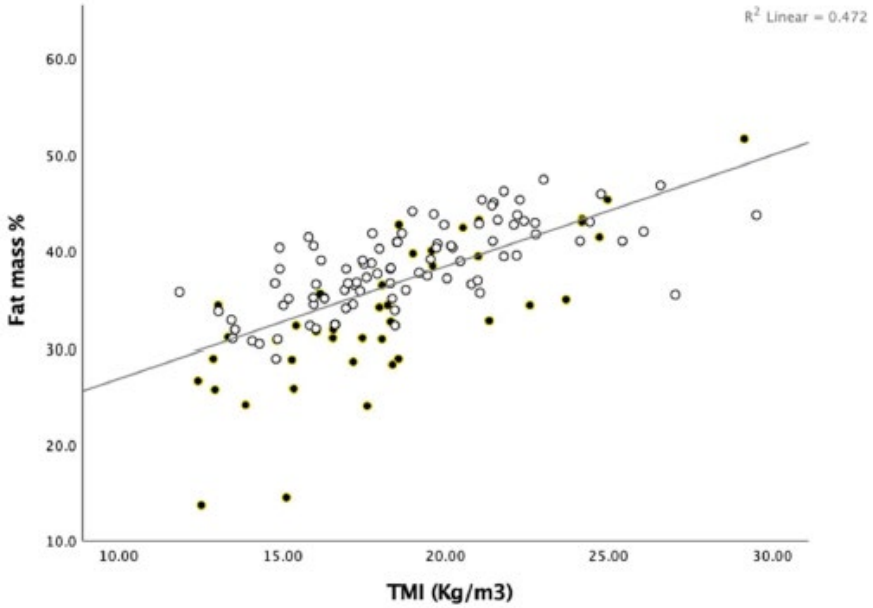


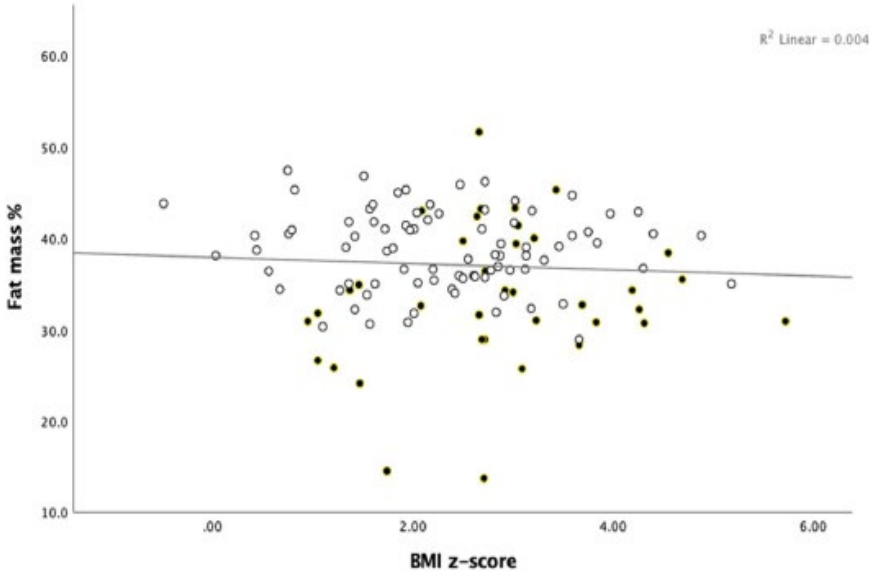
Wang KW et al. Clin Obes. 2018 Feb;8(1):55-67

Question

- Knowing that adiposity correlates more closely with cardiometabolic outcomes when compared to BMI, and that SCBT have a high cardiometabolic burden, are BMI-based measures adequate to assess the fat mass in children?

The BMI-based measures correlate poorly with the fat mass in T2D





Alfaraidi H et al. Scientific Reports; 11(1):9111, 2021

Question

-Do SCBT have higher fat mass (adiposity) than controls?

SCIENTIFIC REPORTS

OPEN

Received: 26 October 2016
Accepted: 20 February 2017
Published: 22 March 2017

Adiposity in childhood brain tumors: A report from the Canadian Study of Determinants of Endometabolic Health in Children (CanDECIDE Study)

Kuan-Wen Wang[1,2,3], Russell J. de Souza[1,4], Adam Fleming[1,2,5], Sheila K. Singh[6,7], Donna L. Johnston[8], Shayna M. Zelcer[9], Shahrad Rod Rassekh[10], Sarah Burrow[11], Katrin Scheinemann[2,12], Lehana Thabane[1,4,13,14,15] & M. Constantine Samaan[1,2,3,4]

SCBT have higher adiposity than non-cancer controls with similar BMI

Variables	Control			CBT			p-value[a]
	Total (n=106) Mean (SD)	Male (n=55) Mean (SD)	Female (n=51) Mean (SD)	Total (n=56) Mean (SD)	Male (n=33) Mean (SD)	Female (n=23) Mean (SD)	
Age (years)	14.0(2.8)	14.0(2.6)	14.0(3.0)	14.7(7.1)	14.8(5.5)	14.5(9.0)	0.589
Sex, No. (%)							
Female	51(48.1)	-	-	23(41.1)	-	-	0.392
Male	55(51.9)	-	-	33(58.9)	-	-	
Height (cm)	161.7(15.3)	166.0(16.8)	157.2(11.9)	150.6(25.2)	155.9(26.1)	143.0(22.3)	0.002
Weight (kg)	59.0(20.8)	64.3(25.0)	53.5(13.3)	52.4(24.1)	55.2(23.0)	48.5(25.5)	0.020
BMI (kg/m2)	22.1(5.6)	22.8(6.6)	21.4(4.1)	21.6(5.5)	21.4(4.4)	21.8(6.8)	0.506
BMI z-score[b]	0.49(1.16)	0.58(1.27)	0.41(1.02)	0.41(1.15)	0.32(1.26)	0.55(0.96)	0.680
BMI category, No. (%)							
BMI%ile<85	69(65.1)	34(61.8)	35(68.6)	36(64.3)	22(66.7)	14(60.9)	0.952
BMI%ile≥85	37(34.9)	21(38.1)	16(31.4)	20(35.7)	11(33.3)	9(39.1)	
Fat mass percentage (%)	22.2(9.0)	19.1(9.0)	25.6(7.8)	25.8(9.6)	23.0(9.4)	29.9(8.6)	0.043
Waist-to-hip ratio	0.82(0.09)	0.84(0.08)	0.80(0.10)	0.87(0.07)	0.86(0.07)	0.88(0.08)	<0.001
Waist-to-height ratio	0.45(0.08)	0.45(0.09)	0.44(0.07)	0.47(0.06)	0.47(0.06)	0.48(0.07)	0.009
Systolic blood pressure (mmHg)	107.2(10.6)	110.4(10.6)	103.7(9.6)	104.0(11.5)	104.1(11.6)	103.9(11.8)	0.069
Diastolic blood pressure (mmHg)	67.6(9.6)	67.1(10.0)	68.1(9.1)	66.3(8.5)	66.2(8.5)	66.4(8.8)	0.432
Physical activity level, No. (%)							
Active	97(91.5)	48(87.3)	49(96.1)	43(76.8)	25(75.8)	18(78.3)	0.009
Inactive	9(8.5)	7(12.7)	2(3.9)	13(23.2)	8(24.2)	5(21.7)	
Total screen time (hours/day)	4.3(2.6)	4.8(2.7)	3.8(2.5)	4.5(2.7)	4.8(2.6)	3.9(2.7)	0.612
Total sleep duration (hours/day)	9.5(1.4)	9.7(1.7)	9.4(1.1)	9.6(1.2)	9.4(1.2)	9.7(1.1)	0.902

Modified from Wang KW et al, 2017

Predictors of adiposity in children with brain tumors

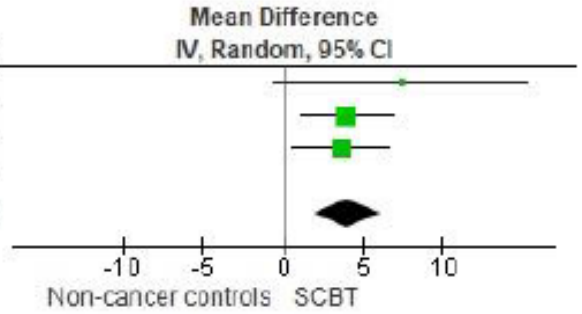
Variables	%FM		WHR		WHtR	
	β (SE)	P-value	β (SE)	P-value	β (SE)	P-value
Age	-0.12 (0.10)	0.23	-0.28 (0.03)	0.29	-0.02 (0.03)	0.50
Sex	0.55 (0.52)	0.30	-0.13 (0.14)	0.36	-0.13 (0.18)	0.46
Puberty	1.11 (0.99)	0.28	0.28 (0.26)	0.29	0.35 (0.34)	0.32
Brain tumor type	-0.33 (0.44)	0.46	-0.06 (0.11)	0.58	0.08 (0.15)	0.61
Brain tumor location	-1.83 (0.80)	0.028	-0.37 (0.21)	0.08	-0.53 (0.27)	0.06
Surgery	0.91 (0.81)	0.27	0.08 (0.21)	0.69	0.20 (0.28)	0.47
Radiotherapy	1.65 (0.79)	0.046	0.08 (0.21)	0.69	0.22 (0.27)	0.43
Chemotherapy	-0.86 (0.74)	0.25	0.06 (0.19)	0.77	-0.02 (0.25)	0.93
Steroids	0.68 (0.62)	0.28	0.04 (0.16)	0.81	0.21 (0.21)	0.32
Prudent diet	0.13(0.33)	0.68	0.06 (0.08)	0.44	0.06 (0.11)	0.62
Western diet	0.15 (0.33)	0.64	0.04 (0.09)	0.64	0.17 (0.11)	0.13
High-protein diet	-0.19 (0.27)	0.48	-0.02 (0.07)	0.76	-0.09(0.09)	0.33
Refined carbohydrate diet	0.38 (0.29)	0.20	0.06 (0.08)	0.43	0.07(0.10)	0.45
Physical inactivity	-0.89 (0.57)	0.12	-0.12 (0.15)	0.42	-0.26 (0.19)	0.19
Screen time	1.08 (1.33)	0.42	0.14 (0.34)	0.68	0.42 (0.46)	0.37
Sleep duration	6.41 (7.24)	0.38	1.77 (1.87)	0.35	1.44 (2.49)	0.57

Modified from Wang KW et al., 2017

Survivors have higher total adiposity vs non-cancer controls

Study or Subgroup	SCBT Mean	SCBT SD	SCBT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Siviero-Miachon 2011	22.3	10.8	16	14.9	9	9	6.7%	7.40 [-0.51, 15.31]
Steinberger 2012	29.9	10.9	82	25.9	13	208	48.1%	4.00 [1.05, 6.95]
Wang 2017	25.8	9.6	56	22.2	9	106	45.2%	3.60 [0.56, 6.64]
Total (95% CI)			**154**			**323**	**100.0%**	**4.05 [2.00, 6.09]**

Heterogeneity: Tau² = 0.00; Chi² = 0.77, df = 2 (P = 0.68); I² = 0%
Test for overall effect: Z = 3.88 (P = 0.0001)



clinical obesity

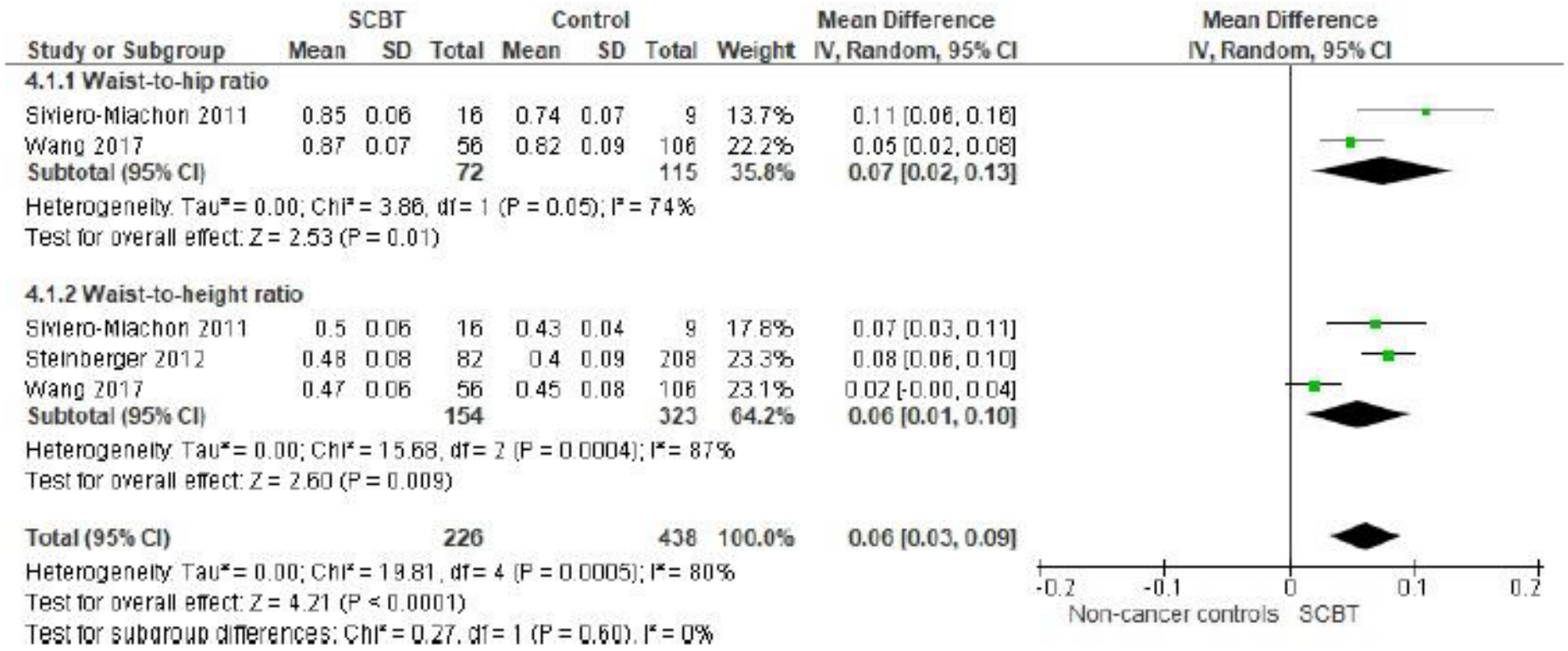
doi: 10.1111/cob.12224

Review

Overweight, obesity and adiposity in survivors of childhood brain tumours: a systematic review and meta-analysis

K-W. Wang[1,2,3], A. Fleming[1,3,4], D. L. Johnston[5], S. M. Zelcer[6], S. R. Rassekh[7], S. Ladhani[1,2], A. Socha[1,2], J. Shinuda[1,2], S. Jaber[1,2], S. Burrow[8], S. K. Singh[9,10], L. Banfield[11], R. J. de Souza[3,12], L. Thabane[3,12,13,14,15] and M. C. Samaan[1,2,3,12]

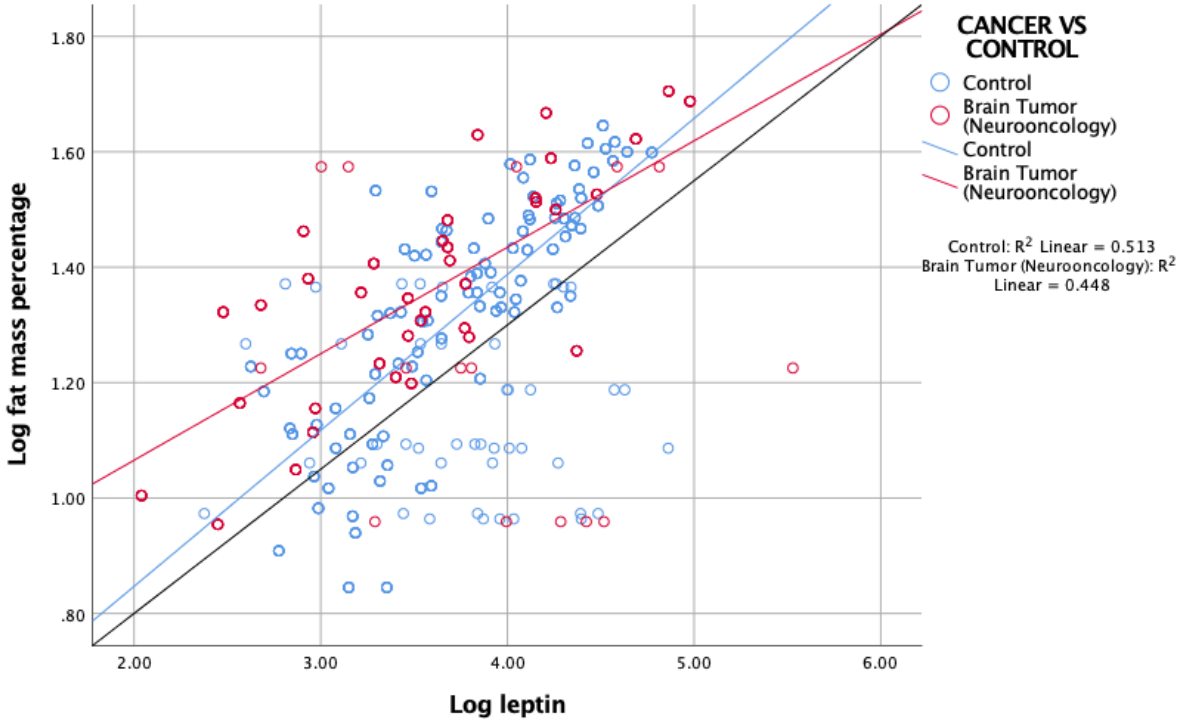
SCBT have higher central adiposity when compared to controls



Study or Subgroup	SCBT Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
4.1.1 Waist-to-hip ratio								
Siviero-Miachon 2011	0.85	0.06	16	0.74	0.07	9	13.7%	0.11 [0.06, 0.16]
Wang 2017	0.87	0.07	56	0.82	0.09	106	22.2%	0.05 [0.02, 0.08]
Subtotal (95% CI)			**72**			115	35.8%	**0.07 [0.02, 0.13]**
Heterogeneity: Tau² = 0.00; Chi² = 3.86, df = 1 (P = 0.05); I² = 74%								
Test for overall effect: Z = 2.53 (P = 0.01)								
4.1.2 Waist-to-height ratio								
Siviero-Miachon 2011	0.5	0.06	16	0.43	0.04	9	17.8%	0.07 [0.03, 0.11]
Steinberger 2012	0.48	0.08	82	0.4	0.09	208	23.3%	0.08 [0.06, 0.10]
Wang 2017	0.47	0.06	56	0.45	0.08	106	23.1%	0.02 [-0.00, 0.04]
Subtotal (95% CI)			**154**			323	64.2%	**0.06 [0.01, 0.10]**
Heterogeneity: Tau² = 0.00; Chi² = 15.68, df = 2 (P = 0.0004); I² = 87%								
Test for overall effect: Z = 2.60 (P = 0.009)								
Total (95% CI)			**226**			438	100.0%	**0.06 [0.03, 0.09]**
Heterogeneity: Tau² = 0.00; Chi² = 19.81, df = 4 (P = 0.0005); I² = 80%								
Test for overall effect: Z = 4.21 (P < 0.0001)								
Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.60), I² = 0%								

Wang KW et al. Clin Obes. 2018 Feb;8(1):55-67

Leptin correlates positively with the fat mass in SCBT



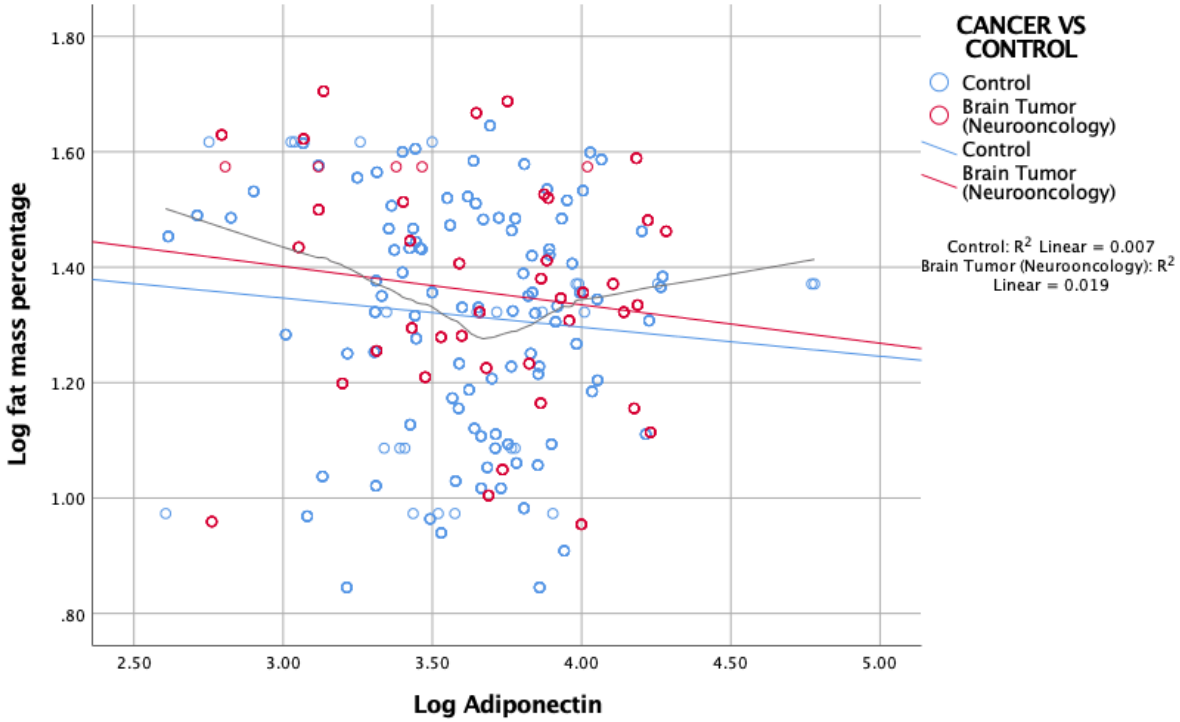
SCIENTIFIC REPORTS
natureresearch

Circulating leptin levels are associated with adiposity in survivors of childhood brain tumors

E. Danielle Sims[1,2], William J. Jennings[1,2], Brianna Empringham[1,2], Adam Fleming[1,3], Carol Portwine[1,3], Donna L. Johnston[4], Shayna M. Zelcer[5], Shahrad Rod Rassekh[6], Sarah Burrow[7], Lehana Thabane[6,9,10,11] & M. Constantine Samaan[1,2,8*]

Adopted from Sims et al. Scientific Reports, 2020

Adiponectin correlates negatively with the fat mass in SCBT and controls



scientific reports

OPEN

High molecular weight adiponectin levels are inversely associated with adiposity in pediatric brain tumor survivors

Rebecca Ronsley[1], Shahrad Rod Rassekh[1], Adam Fleming[2,3], Brianna Empringham[2,4], William Jennings[2,4], Carol Portwine[2,3], Sarah Burrow[5], Shayna Zelcer[6], Donna L. Johnston[7], Lehana Thabane[8,9,10,11] & M. Constantine Samaan[2,4,8,12]✉

Adapted from Ronsley et al. Scientific Reports, 2021

Question

- Are there effective interventions to treat obesity now?

obesity reviews

doi: 10.1111/obr.12534

Obesity Treatment

The effectiveness of interventions to treat hypothalamic obesity in survivors of childhood brain tumours: a systematic review

K-W. Wang,[1,2] R. Chau,[1,2] A. Fleming,[1,3] L. Banfield,[4] S. K. Singh,[5,6] D. L. Johnston,[7] S. M. Zelcer,[8] S. R. Rassekh,[9] S. Burrow,[10] M. Valencia,[1,2] R. J. de Souza,[11] L. Thabane[11,12,13,14] and M. C. Samaan[1,2,11]

Lifestyle and pharmacotherapy in SCBT

Author (country, year, study design)	Sample size (M:F)	Duration of intervention	Pre BMI z-score	Post BMI z-score	p-value
Lifestyle intervention					
Rakhshani et al. (Canada, 2010, uncontrolled before-after)	39 (16:23)	Frequency of once per month to once every 6 months at patients' choices Patient attended an average of 3 visits	Change from brain tumor diagnosis to first visit 0.4 (-2.1 to 2.2)	Change from first to last visit 0.0 (-5.2 to 0.5)	ns
Sterkenburg et al. (Germany, 2014, retrospective cohort)	31 (12:19)	39 days (20 days to 4.5 months)	1.3 (-1.1 to 7.0)	4.9 (-0.2 to 13.13)	NR
Pharmacotherapy					
Danielsson et al. (Sweden, 2007, RCT)	5 (2:3)	**Sibutramine** 20 weeks	4.1 (3.2 to 7.1)	3.7 (2.8 to 6.6)	NR
Ismail et al. (Australia, 2006, uncontrolled before-after)	12 (5:7)	**Dexamphetamine** 14 (6 to 63) months	NR	Median change in BMI z-score -0.7 in boys -0.4 in girls	NR
Kalina et al. (Poland, 2015, uncontrolled before-after)	22 (10:12) Only ten of them received the intervention (sex distribution unknown)	**Metformin + fenofibrate** 6 months	1.9 (1.2 to 2.7)	1.9 (1.3 to 2.6)	ns
Lomenick et al. (USA, 2016, uncontrolled before-after)	3 (0:3)	**Exenatide** 50 weeks	Weight 133.1 (115.7 to 225.5)	Weight 127.7 (117.3 to 221.8)	NR
Lustig et al. (USA, 2003, RCT)	10 (6:4) One of them withdrew early due to tumor recurrence	**Octreotide** 6 months	BMI 37.4±2.5	BMI 37.2±2.5	NR
Mason et al. (USA, 2002, uncontrolled before-after)	5 (3:2)	**Dexamphetamine** 24 months	BMI 32±2.8	BMI 31±3.3	ns

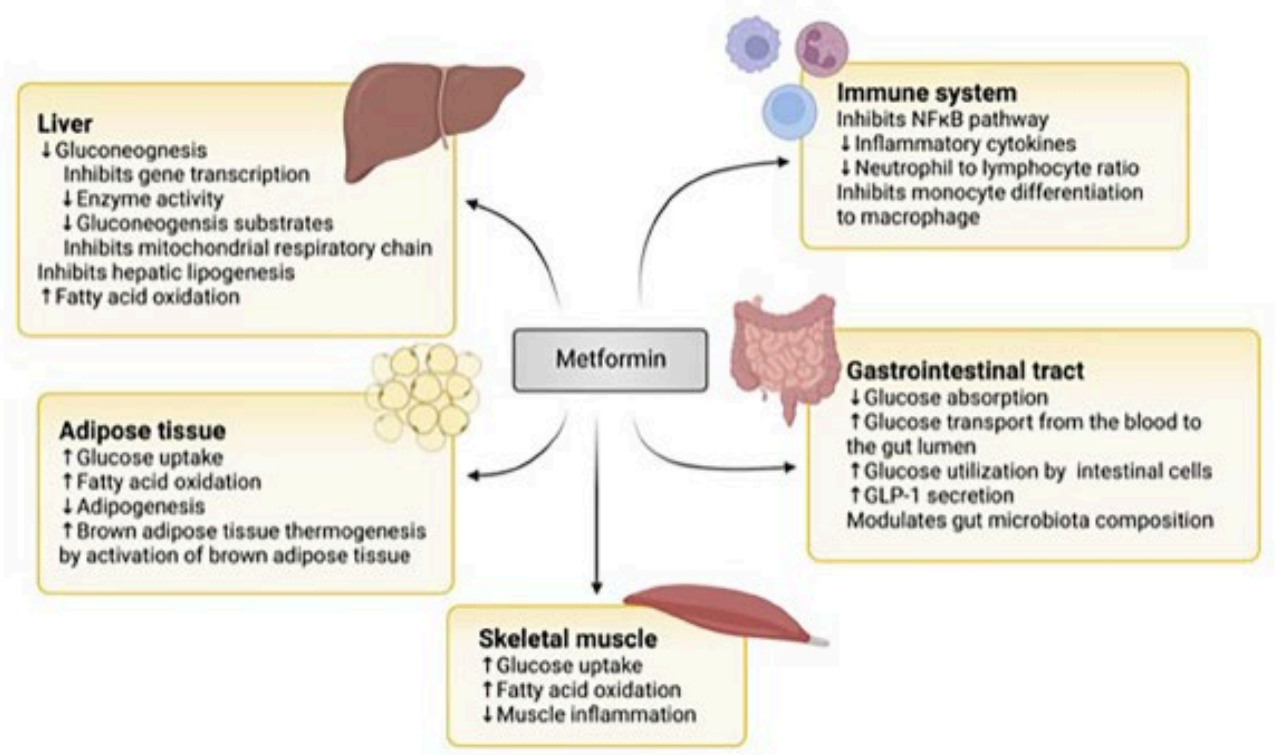
Wang K.W et al. Obesity Reviews, 18(8):899-914, 2017

Bariatric surgery in SCBT

Author (country, year, study design)	Sample size (M:F)	Duration of intervention	Pre BMI z-score	Post BMI z-score	p-value
Bariatric Surgery					
Muller et al. (Germany, 2007 and 2011, uncontrolled before-after)	3 (1:2)	**Adjustable LAGB** Follow-up period 2007: 3 (1.5 to 4.5) years 2011: 7.1 (5.3 to 9.1) years	11.4 (10.3 to 13.9)	2007 9.7 (9.5 to 9.9) 2011 10.2 (10.2 to 13.9)	NR
Weismann et al. (Germany, 2013, uncontrolled before-after)	9 (2:7)	**LAGB, SG, GB** Median follow-up LAGB: 5.5 years SG: 2 years GB: 3 years	NR	% weight change LAGB: 5% SG: 3% GB: -28%	NR

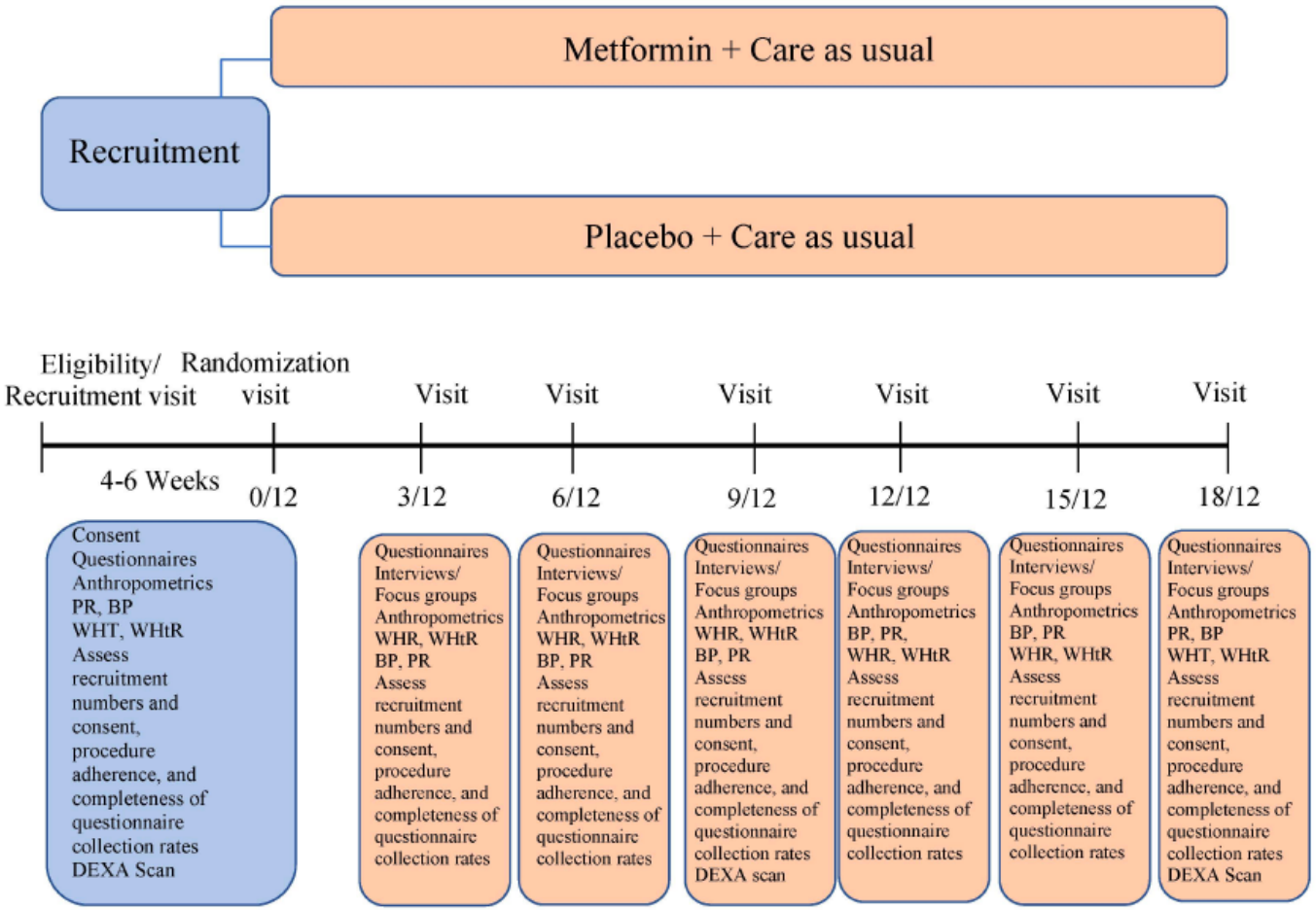
Wang K.W et al. Obesity Reviews, 18(8):899-914, 2017

Metformin



Alfaraidi H et al. Front Endocrinol. 13: 1072879, 2023

Trial plan


Metformin + Care as usual
Recruitment
Placebo + Care as usual
Eligibility/ Recruitment visit
Randomization visit
Visit
Visit
Visit
Visit
Visit
Visit
4-6 Weeks
0/12
3/12
6/12
9/12
12/12
15/12
18/12
Consent
Questionnaires
Anthropometrics
PR, BP
WHT, WHtR
Assess recruitment numbers and consent, procedure adherence, and completeness of questionnaire collection rates
DEXA Scan
Questionnaires
Interviews/ Focus groups
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DEXA Scan

Conclusions

- SCBT have excess adiposity with an equivalent BMI profile to controls
- Total adiposity is driven by radiotherapy and tumor location
- There is no high-quality evidence for effective obesity treatments in SCBT, but this may change with new approaches to obesity treatment like metformin

Translational Research in Pediatrics Group

Acknowledgments

- **Translational Research in Pediatrics Group**

Clinical teams

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Ishan Aditya

Erin Fu

Maggie Hou

Emily Yang

Sabrina Wang

Collaborators

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