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; <u>https://doi.org/10.3390/biology8020023</u>

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

BMI

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}

Canadian Study of Determinants OPEN 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. Johnston⁵, S. M. Zelcer⁶, S. R. Rassekh⁷, S. Ladhani^{1,2}, A. Socha^{1,2}, J. Shinuda^{1,2}, S. Jaber^{1,2}, S. Burrow⁸, S. K. Singh^{9,10}, L. Banfield¹¹, 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 <u>non-cancer controls</u>

Ctudy or Cubaroup	Drovalanco	CE.	Woight	Prevalence	Prevalence
1 4 4 Overweight	Prevalence	3E	weight	IV, Kandom, 95% CI	IV, Kandom, 95% CI
1.4.1 Over weight	00.7	0.00	40.70	00 70 100 05 00 45	
Meacham 2005	32.1	0.23	12.7%	32.70 [32.25, 33.15]	
Warner 2014	31.1	0.63	12.6%	31.10 [29.87, 32.33]	
Subiolal (95% CI)	1.00.047-5	00 46	23.3%	32.01 [30.45, 33.50]	,
Heterogeneity: Tau* = Teet for everall effect	= 1.06; Chin= 5	.69, 01	= 1 (P = 1	J.UZ); I*= 82%	
lesi for overall effect	7 = 40.38 (P 4				
1.4.2 Obesity					
Meacham 2005	16.6	0.18	12.7%	16.60 [16.25, 16.95]	
Warner 2014	17	0.51	12.6%	17.00 [16.00, 18.00]	
Subtotal (95% CI)			25.3%	16.64 [16.31, 16.98]	1
Heterogeneity: Tau ² =	= 0.00; Chi ² = 0	.55, df	= 1 (P = (0.46); I ² = 0%	
Test for overall effect	Z = 98.06 (P <	0.000	01)		
1.4.3 Overweight/Ob	esity				
	oung				
Brouwer 2012	26.3	1.8	12.5%	26.30 [22.77, 29.83]	+
Brouwer 2012 Meacham 2005	26.3 49.3	1.8 0.25	12.5% 12.7%	26.30 [22.77, 29.83] 49.30 [48.81, 49.79]	÷.,
Brouwer 2012 Meacham 2005 Wang 2017	26.3 49.3 34.9	1.8 0.25 4.6	12.5% 12.7% 11.6%	26.30 [22.77, 29.83] 49.30 [48.81, 49.79] 34.90 [25.88, 43.92]	· ·
Brouwer 2012 Meacham 2005 Wang 2017 Warner 2014	26.3 49.3 34.9 48.1	1.8 0.25 4.6 0.68	12.5% 12.7% 11.6% 12.6%	26.30 [22.77, 29.83] 49.30 [48.81, 49.79] 34.90 [25.88, 43.92] 48.10 [46.77, 49.43]	: :
Brouwer 2012 Meacham 2005 Wang 2017 Warner 2014 Subtotal (95% CI)	26.3 49.3 34.9 48.1	1.8 0.25 4.6 0.68	12.5% 12.7% 11.6% 12.6% 49.4%	26.30 [22.77, 29.83] 49.30 [48.81, 49.79] 34.90 [25.88, 43.92] 48.10 [46.77, 49.43] 40.40 [34.00, 46.79]	· · · ·
Brouwer 2012 Meacham 2005 Wang 2017 Warner 2014 Subtotal (95% CI) Heterogeneity: Tau ² =	26.3 49.3 34.9 48.1 = 37.72; Chi ² =	1.8 0.25 4.6 0.68 170.3	12.5% 12.7% 11.6% 12.6% 49.4% 7, df = 3 (F	26.30 [22.77, 29.83] 49.30 [48.81, 49.79] 34.90 [25.88, 43.92] 48.10 [46.77, 49.43] 40.40 [34.00, 46.79] P < 0.00001); ² = 98%	' '
Brouwer 2012 Meacham 2005 Wang 2017 Warner 2014 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect:	26.3 49.3 34.9 48.1 = 37.72; Chi ² = : Z = 12.39 (P <	1.8 0.25 4.6 0.68 170.3 0.000	12.5% 12.7% 11.6% 12.6% 49.4% 7, df = 3 (F 01)	26.30 [22.77, 29.83] 49.30 [48.81, 49.79] 34.90 [25.88, 43.92] 48.10 [46.77, 49.43] 40.40 [34.00, 46.79] P < 0.00001); ² = 98%	' '
Brouwer 2012 Meacham 2005 Wang 2017 Warner 2014 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI)	26.3 49.3 34.9 48.1 = 37.72; Chi ² = : Z = 12.39 (P <	1.8 0.25 4.6 0.68 170.33	12.5% 12.7% 11.6% 12.6% 49.4% 7, df= 3 (f 01)	26.30 [22.77, 29.83] 49.30 [48.81, 49.79] 34.90 [25.88, 43.92] 48.10 [46.77, 49.43] 40.40 [34.00, 46.79] P < 0.00001); ² = 98% 31.98 [21.11, 42.84]	* * *
Brouwer 2012 Meacham 2005 Wang 2017 Warner 2014 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² =	26.3 49.3 34.9 48.1 = 37.72; Chi ² = : Z = 12.39 (P <	1.8 0.25 4.6 0.68 170.33 0.000	12.5% 12.7% 11.6% 12.6% 49.4% 7, df = 3 (F 01) 100.0% 3.59 df =	26.30 [22.77, 29.83] 49.30 [48.81, 49.79] 34.90 [25.88, 43.92] 48.10 [46.77, 49.43] 40.40 [34.00, 46.79] P < 0.00001); I ² = 98% 31.98 [21.11, 42.84] 7 (P < 0.00001); I ² = 100	* * *
Brouwer 2012 Meacham 2005 Wang 2017 Warner 2014 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect	26.3 49.3 34.9 48.1 37.72; Chi ² = Z = 12.39 (P <	1.8 0.25 4.6 0.68 170.33 0.000	12.5% 12.7% 11.6% 12.6% 49.4% 7, df= 3 (f 01) 100.0% 3.59, df=	26.30 [22.77, 29.83] 49.30 [48.81, 49.79] 34.90 [25.88, 43.92] 48.10 [46.77, 49.43] 40.40 [34.00, 46.79] P < 0.00001); ² = 98% 31.98 [21.11, 42.84] 57 (P < 0.00001); ² = 100 ⁴	

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

The prevalence of obesity in SCBT

No CP

CP

Study or Subgroup Prevalence SE Weight IV, Random, 95% Cl IV, Random, 95% Cl 121 All Brain Tumors Cl 20.5 6.1 3.3% 20.50 [8.54, 32.46]					Prevalence	Prevalence
1.2.1 All Brain Tumors Felicetti 2005 20.5 6.1 3.3% 20.50 [8.54, 32.46] Guernes Hidalgo 2014 28.9 7.4 3.2% 28.90 [14.40, 43.40] Hansen 2014 20.2 6.6 3.2% 29.20 [16.26, 42.14] Miyoshi 2008 23.1 8.3 3.1% 23.10 [6.8, 33.37] Pietlia 2009 7.7 3.7 3.5% 7.70 [0.45, 14.95] Warner 2014 22.6 3.4 3.5% 36.10 [28.65, 43.55] Subtotal (95% CI) 23.2% 23.75 [15.28, 32.22] Heterogeneity: Tau" = 99.05; Chi ^a = 30.67, df = 6 ($P < 0.0001$); $P = 80\%$ 1.2.2 NO Craniopharyngioma Gan 2015 32.5 3.6 3.5% 32.50 [25.44, 39.56] Meacham 2005 15 1.2 3.6% 15.00 [12.65, 17.35] Subtotal (95% CI) 13.9% 17.86 [8.97, 26.7] Heterogeneity: Tau" = 71.32; Chi ^a = 35.17, df = 3 ($P < 0.00001$); $P = 91\%$ 1.2.3 Craniopharyngioma Amayii 2017 33.3 9.6 2.9% 33.30 [14.48, 52.12] Crom 2010 23.5 5.9 3.3% 25.50 [19.4, 43.506] de Vile 1996 55.7 6.2 3.3% 58.70 [45.55, 70.85] Gautite 2012 44.3 6.4 3.3% 44.30 [31.76, 56.84] Holmer 2009 50 7.7 3.1% 55.00 [34.91, 65.09] Holmer 2009 50 7.7 3.1% 55.00 [34.91, 65.09] Kima 2014 72 9 3.0% 72.00 [45.48, 89.64] Muller 2012 44.3 6.4 3.3% 45.50 [29.4, 43.86] Muller 2013 73.3 6.4 3.3% 57.50 [29.4, 64.36] Muller 2014 72 9 3.3% 57.50 [29.4, 64.36] Muller 2013 43.8 12.4 2.6% 43.80 (19.5, 66.84] Holmer 2009 50 7.7 3.1% 55.00 [34.91, 65.09] Muller 2013 73.3 6.4 3.3% 57.90 [25.36, 50.44] Muller 2013 43.8 12.4 2.6% 43.80 [19.50, 66.10] Holmer 2009 50 7.7 3.78 55.00 [29.4, 64.38] Muller 2013 6.6.1 4.5 3.4% 66.10 [57.28, 74.92] Muller 2013 6.6.1 4.5 3.4% 66.10 [57.28, 74.92] Muller 2013 6.51 8.2.2% 55.00 [28.6, 74.19] Muller 2013 6.51 8.2.2% 55.00 [28.6, 74.19] Muller 2013 6.51 8.2.2% 55.00 [28.6, 74.32] Heterogeneity: Tau" = 153.35; Chi ^a = 77.85, df = 20 (P < 0.00001); P = 74% Test for overail effect; Z = 15.52 (P < 0.00001) Heterogeneity: Tau" = 153.35; Chi ^a = 77.85, df = 20 (P < 0.00001); P = 74% Test for overail effect; Z = 15.52 (P < 0.00001)	Study or Subgroup	Prevalence	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Felicetil 2005 20.5 6.1 3.3% 20.50 [8.54, 32.46] Guernes Hidalgo 2014 28.9 7.4 3.2% 28.90 [14.40, 43.40] Hansen 2014 29.2 6.6 3.2% 29.20 [14.40, 43.40] Hansen 2014 29.2 6.6 3.2% 29.20 [16.26, 42.14] Miyoshi 2006 23.1 8.3 3.1% 23.10 [0.45, 14.95] Warner 2014 22.6 3.4 3.5% 22.60 [15.94, 29.26] Wilson 2015 36.1 3.8 3.5% 32.50 [25.44, 39.56] Subtotal (95% CI) 23.27 df = 6 ($P < 0.0001$); $P = 80\%$ Heterogeneity: Tau" = 99.05; Ch ² = 30.67, df = 6 ($P < 0.0001$); $P = 80\%$ 1.2.2 No Craniopharyngioma Gan 2015 32.5 3.6 3.5% 18.50 [25.44, 39.56] Meacham 2005 15 1.2 3.6% 15.00 [12.65, 17.35] Schutte 2010 18.5 5.3 3.4% 18.50 [8.11, 28.89] Shaltiln 2011 7 2.4 3.5% 7.00 [2.30, 11.70] Subtotal (95% CI) 7.4 df = 3 ($P < 0.00001$); $P = 91\%$ 1.2.3 Craniopharyngioma Armayin 2017 33.3 9.6 2.9% 33.30 [14.48, 52.12] Crom 2010 23.5 5.9 3.3% 23.50 [11.94, 35.66] de Vile 1996 58.7 6.2 3.3% 58.70 [46.55, 70.85] Gautier 2012 44.3 6.4 3.3% 53.30 [31.76, 56.84] Hallioglu 2016 53.3 7.4 3.2% 53.30 [38.80, 67.80] Holmer 2009 50 7.7 3.1% 50.00 [34.91, 65.50] Khan 2014 72 9 3.0% 72.00 [54.36, 89.64] Hallioglu 2016 45.3 3 6.4 3.3% 53.30 [40.76, 65.84] Halliogu 2013 43.8 12.4 2.6% 73.30 [25.36, 50.44] Halliogu 2013 43.8 12.4 2.6% 73.30 [25.36, 50.44] Halliogu 2013 43.8 12.4 2.5% 72.70 [46.44, 98.96] Kunz 2010 72.7 13.4 2.5% 57.00 [25.36, 50.44] Halliogu 2013 43.8 12.4 2.6% 43.80 [19.50, 68.10] Halliogu 2013 43.8 12.4 2.6% 43.80 [19.50, 68.10] Halliogu 2013 45.8 7.3 3.2% 43.50 [29.19, 57.81] Muller 2003 53.3 6.4 3.3% 53.30 [40.76, 65.84] Pedreira 2006 50 11.8 2.2% 50.00 [26.87, 73.13] Qi 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Heterogeneity: Tau" = 153.35; Chi" = 77.85, df = 20 (P < 0.00001); I ^a = 74% Test for overall effect; Z = 16.52 (P < 0.00001) Heterogeneity: Tau" = 405.88; Chi" = 590.52, df = 31 (P < 0.00001); I ^a = 74% Test for overall effect; Z = 16.52 (P < 0.00001); I ^a = 74% Total (95% CI) 100.9% 42.44 [34.96, 49.20] Heterogeneity: Tau" = 405.88; Chi" = 590.52, df = 31 (P < 0.00001); I	1.2.1 All Brain Tumors					
Guemes Hidalgo 2014 28.9 7.4 3.2% 28.90 [14.40, 43.40] Hansen 2014 29.2 6.6 3.2% 29.20 [16.26, 42.14] Miyoshi 2008 7.7 3.5% 7.70 [0.45, 14.95] Warner 2014 22.6 3.4 3.5% 23.00 [16.34, 29.26] Wilson 2015 36.1 3.8 3.5% 23.60 [16.34, 29.26] Heterogeneity: Tau" = 99.05; Ch ² = 30.67, df = 6 (P < 0.0001); I ^a = 80% 1.2.2 No Craniopharyngioma Gan 2015 32.5 3.6 3.5% 32.50 [25.44, 39.56] Meacham 2005 15 1.2 3.6% 15.00 [24.65, 17.35] Shaltin 2011 7 2.4 3.5% 7.00 [2.30, 11.70] Shaltin 2011 7 2.4 3.5% 7.00 [2.30, 11.70] Heterogeneity: Tau" = 71.32; Ch ² = 35.17, df = 3 (P < 0.00001); I ^a = 91% 1.2.3 Craniopharyngioma Amayii 2017 33.3 9.6 2.9% 33.30 [14.48, 52.12] Crom 2010 23.5 5.9 3.3% 25.00 [24.64, 49.86] de Vile 1996 58.7 $6.2.2$ 3.3% 58.70 [46.55, 70.85] Gautier 2012 44.3 6.4 3.3% 44.30 [31.76, 56.84] Holmer 2009 50 7.7 3.1% 55.00 [34.91, 65.09] Kima 2014 72 9 3.0% 72.70 [46.44, 98.96] Kima 2014 72 9 3.3% 64. 3.3% 67.00 [24.9, 74.81] Holmer 2009 50 7.7 3.1% 55.00 [28.7, 74.31] Holmer 2009 50 7.7.7 3.1% 55.00 [28.7, 74.31] Holmer 2009 50 7.7.7 3.1% 55.00 [28.7, 73.13] Muller 2013 72.7 13.4 2.5% 72.70 [46.44, 98.96] Muller 2014 72 9 3.3% 64. 3.3% 64.30 [0.9, 57.81] Muller 2013 73.6 5.3% 55.30 (29.9, 9, 57.81] Muller 2013 73.8 5.3% 55.30 (28.0, 67.81] Heterogeneity: Tau" = 153.35; Ch ³ = 77.85, df = 20 (P < 0.00001); I ^a = 74% Tath 2013 60.1 1.8 2.7% 50.00 [28.8, 7.49.2] Anth 2013 60.1 1.8 2.7\% 53.00 [28.8, 7.49.2] Heterogeneity: Tau" = 153.35; Ch ³ = 77.85, df = 20 (P < 0.00001); I ^a = 74% Total (95% Cl) $(22.9\%$ 54.0 (21.4, 95.68, 94.74] Heterogeneity: Tau" = 153.35; Ch ³ = 77.85, df = 20 (P < 0.00001); I ^a = 74% Total (95% Cl) $(22.9\%$ 54.0 (21.4, 95.68, 94.74] Heterogeneity: Tau" = 150.58; Ch ³ = 77.85, df = 20 (P < 0.00001); I ^a = 74%	Felicetti 2005	20.5	6.1	3.3%	20.50 [8.54, 32.46]	_ _
Hansen 2014 29.2 6.6 3.2% 29.20 [16.26, 42.14] Miyoshi 2006 23.1 8.3 3.1% 23.10 [6.83, 39.37] Pietlia 2009 7.7 3.7 3.5% 7.70 [0.45, 14.95] Warner 2014 22.6 3.4 3.5% 22.60 [15.94, 29.26] Wilson 2015 36.1 3.8 3.5% 23.70 [28.56, 43.55] Subtotal (95% CI) 23.2% 23.75 [15.28, 32.22] Heterogeneity: Tau ² = 99.05; Chi ² = 30.67, df = 6 ($P < 0.0001$]; $P = 80\%$ Future 2010 18.5 5.3 3.4% 18.50 [8.11, 28.88] Schulte 2010 18.5 5.3 3.4% 18.50 [25.44, 39.56] Meacham 2005 15 1.2 3.6% 15.00 [12.65, 17.35] Schulte 2010 18.5 5.3 3.4% 18.50 [8.11, 28.88] Shaltin 2011 7 2.4 3.5% 7.00 [2.30, 11.70] Subtotal (95% CI) 13.9% 17.86 [5.97, 26.75] Heterogeneity: Tau ² = 71.32; Chi ² = 35.17, df = 3 ($P < 0.00001$); $P = 91\%$ 1.23 Craniopharyngioma Analyti 2017 33.3 9.6 2.9% 33.30 [14.48, 52.12] Crom 2010 23.5 5.9 3.3% 23.50 [11.94, 35.06] de Vile 1996 58.7 6.2 3.3% 58.70 [46.55, 70.85] Gautier 2012 44.3 6.4 3.3% 44.30 [31.76, 65.84] Hallioglu 2016 53.3 7.4 3.2% 53.30 [38.80, 67.80] Khan 2014 72 9 3.0% 72.20 [54.44, 98.96] Kin 2010 72.7 13.4 2.5% 72.70 [46.44, 98.96] Kin 2010 72.7 13.4 2.5% 50.00 [34.91, 65.06] Muller 2003 50 17.8 3.3 0 [62.46, 43.6] Muller 2003 53.3 6.4 3.3% 53.30 [10.57, 85.74] Pedreira 2006 50 11.8 2.7% 50.00 [28.07, 73.13] Qi 2013 66.1 4.5 3.4% 63.01 [95.06, 86.10] Lek 2010 43.5 7.3 3.2% 53.00 [27.8, 65.84] Pedreira 2006 50 11.8 2.7% 50.00 [28.07, 73.13] Qi 2013 66.1 4.5 3.4% 63.03 [19.50, 68.10] Lek 2010 43.5 7.3 3.2% 53.00 [28.07, 68.58] Muller 2003 53.3 6.4 3.3% 53.30 [02.78, 65.84] Pedreira 2006 50 11.8 2.7% 50.00 [28.07, 74.31] Pedreira 2006 50 11.8 2.7% 50.00 [35.08, 80.15] Sintvasan 2004 53.3 12.9 2.5% 53.00 [28.08, 15] Sintvasan 2004 53.3 12.9 2.5% 53.00 [35.08, 84.02] 4.1.2.2% 53.00 [35.08, 84.02] 5.1.2.2% 53.00 [35.08, 84.02] 4.1.2.2% 53.00 [35.08, 84.02] 4.1.2.2% 53.00 [35.08, 84.02] 4.1.2.2% 53.00 [35.08, 84.02] 4.1.2	Guernes Hidalgo 2014	28.9	7.4	3.2%	28.90 [14.40, 43.40]	
Miyoshi 2008 23.1 8.3 3.1% 23.10 (6.3) 99.37] Pietila 2009 7.7 3.7 3.5% 7.70 [0.45, 14.95] Wilson 2015 36.1 3.8 3.5% 22.60 [15.94, 29.26] Wilson 2015 36.1 3.8 3.5% 22.60 [15.94, 29.26] Evelocid (95% CI) 23.2% 23.75 [15.28, 32.22] Heterogeneity: Tau ² = 99.05; Chi ² = 30.67, df = 6 (P < 0.0001); I ² = 80% 1.2.2 No Craniopharyngioma Gan 2015 32.5 3.6 3.5% 32.50 [25.44, 39.56] Meacham 2005 15 1.2 3.6% 15.00 [12.65, 17.35] Schulte 2010 18.5 5.3 3.4% 18.50 [8.11, 28.89] Shaltin 2011 7 24 3.5% 7.00 [2.30, 11.70] Subtotal (95% CI) 13.9% 17.86 [8.97, 26.75] Heterogeneity: Tau ² = 71.32; Chi ² = 35.17, df = 3 (P < 0.00001); I ² = 91% 1.2.3 Craniopharyngioma Amayiri 2017 33.3 9.6 2.9% 33.30 [14.48, 52.12] Crom 2010 23.5 5.9 3.3% 23.50 [14.94, 35.06] Gautier 2012 44.3 6.4 3.3% 44.30 [31.76, 56.84] Haliloglu 2016 53.3 7.4 3.2% 53.30 [38.80, 67.80] Halilogu 2016 53.3 7.4 3.2% 53.30 [38.80, 67.80] Halilogu 2013 43.8 12.4 2.6% 43.80 [19.50, 68.10] Lek 2010 43.5 7.3 3.6 3.5% 57.30 [50.24, 64.36] Muller 2003 50 17.7 3.4% 53.30 [29.19, 57.81] Muller 2003 50 17.8 3.30 (25.36, 50.44] Pedreira 2006 50 11.8 2.7% 50.00 [28.37, 73.13] Qi 2013 66.1 4.5 3.3 7.4 3.2% 53.30 [28.06, 67.80] Muller 2003 53.3 6.4 3.3% 53.30 [42.4, 26.80] Muller 2003 53.3 6.4 3.3% 53.30 [28.0, 27.81] Muller 2003 53.3 6.4 3.3% 53.30 [28.0, 27.81] Muller 2003 53.3 6.4 3.3% 53.00 [26.23, 100.00] Sorva 1988 58 11.3 2.7% 58.00 [57.28, 78.1] Muller 2031 65.1 1.8 2.7% 58.00 [57.28, 78.1] Muller 2033 65.1 1.8 2.2% 53.00 [28.8, 80.15] Srinvasan 2004 53.3 12.9 2.5% 53.30 [28.0, 47.4] Winchon 2009 70.5 6.9 3.2% 70.50 [58.88, 40.2] Subtotal (95% CI) 62.29% 54.40 (47.95, 68.61] Heterogeneity: Tau ² = 16.53.5C Ch ² = 77.85, df = 20 (P < 0.00001); I ² = 74\% Total (95% CI) 100.0% 42.44 [34.96, 49.92] Heterogeneity: Tau ² = 405.88; Chi ² = 590.52, df = 31 (P < 0.00001); I ² = 95\%	Hansen 2014	29.2	6.6	3.2%	29.20 [16.26, 42.14]	
Piefai 2009 7.7 3.7 3.5% 7.70 [0.45, 14.95] Warner 2014 22.6 3.4 3.5% 22.00 [15.94, 29.26] Wilson 2015 36.1 3.8 3.5% 36.10 [28.65, 13.55] 23.2% 23.7% [15.28, 32.22] Heterogeneity: Tau ² = 99.05; Chi ² = 30.67, df = 6 ($P < 0.0001$); l ² = 80% Teleforgeneity: Tau ² = 99.05; Chi ² = 30.67, df = 6 ($P < 0.0001$); l ² = 80% Tau ² = 99.05; Chi ² = 30.67, df = 6 ($P < 0.0001$); l ² = 80% Tau ² = 99.05; Chi ² = 30.67, df = 6 ($P < 0.0001$); l ² = 80% Tau ² = 99.05; Chi ² = 30.67, df = 6 ($P < 0.0001$); l ² = 80% Tau ² = 99.05; Chi ² = 35.17, df = 3 ($P < 0.0001$); l ² = 91% Tau ² = 71.32; Chi ² = 35.17, df = 3 ($P < 0.0001$); l ² = 91% Heterogeneity: Tau ² = 71.32; Chi ² = 35.17, df = 3 ($P < 0.0001$); l ² = 91% Tau ² = 71.32; Chi ² = 35.17, df = 3 ($P < 0.0001$); l ² = 91% Tau ³ = 71.32; Chi ² = 35.17, df = 3 ($P < 0.0001$); l ² = 91% Tau ³ = 71.32; Chi ² = 35.17, df = 3 ($P < 0.0001$); l ² = 91% Tau ³ = 71.32; Chi ² = 35.17, df = 3 ($P < 0.0001$); l ² = 91% Tau ³ = 71.32; Chi ² = 35.17, df = 3 ($P < 0.0001$; l ² = 91% Tau ³ = 71.32; Chi ² = 35.17, df = 3 ($P < 0.0001$; l ² = 91% Tau ³ = 71.32; Chi ² = 35.17, df = 3 ($P < 0.0001$; l ² = 91% Tau ³ = 71.32; Chi ² = 35.17, df = 3 ($P < 0.00001$; l ² = 91% Tau ³ = 71.32; Chi ² = 71.32; Chi ² = 35.17, df = 3 ($P < 0.00001$; l ² = 91% Tau ³ = 71.32; Chi ² = 71.32; Chi ² = 20, f ² = 30.68; Ch ³ = 30, f ³ = 70, f ³ = 66, f ³ = 10, f ³ = 66, f ³ = 10,	Miyoshi 2008	23.1	8.3	3.1%	23.10 [6.83, 39.37]	_ _
Warner 2014 22.6 3.4 3.5% 22.60 [$15.94, 29.26$] Wilson 2015 36.1 3.8 3.5% 36.10 [$28.66, 43.55$] Subtotal (95% CI) 23.2% 23.75 [$15.28, 32.22$] Heterogeneity: Tau ² = 99.05; Ch ² = 30.67, df = 6 (P < 0.0001); P = 80% 1.2.2 No Craniopharyngioma Gan 2015 32.5 3.6 3.5% 32.50 [$25.44, 39.56$] Meacham 2005 15 1.2 3.6% 15.00 [$12.65, 17.35$] Subtotal (95% CI) 13.9% 17.86 [$15.77, 26.75$] Heterogeneity: Tau ² = 71.32; Ch ² = 35.17, df = 3 (P < 0.00001); P = 91% 1.2.3 Craniopharyngioma Amayiri 2017 33.3 9.6 2.9% 33.30 [$14.48, 52.12$] Crom 2010 23.5 5.9 3.3% 23.50 [$11.94, 35.06$] Gautier 2012 44.3 6.4 3.3% 44.30 [$31.76, 56.84$] Halloglu 2016 53.3 7.4 3.2% 53.30 [$38.80, 67.80$] Halloglu 2016 53.3 7.4 3.2% 53.30 [$38.80, 67.80$] Halloglu 2016 53.3 7.4 3.2% 53.30 [$38.80, 67.80$] Halloglu 2016 53.3 7.4 3.2% 53.00 [$34.97, 65.84$] Halloglu 2016 53.3 7.4 3.2% 53.00 [$34.97, 65.84$] Halloglu 2016 53.3 6.4 3.3% 53.00 [$44.78, 57.81$] Muller 2001 43.8 12.4 2.6% 43.80 [$19.50, 68.10$] Heterogeneity: Tau ² = 153.35; Ch ² = 77.85, df = 20 (P < 0.00001); P = 774% Test for overall effect: Z = 16.52 (P < 0.00001) Total (95% CI) 100.0% 42.44 [$34.96, 49.92$] Heterogeneity: Tau ² = 405.88; Ch ² = 590.52, df = 31 (P < 0.00001); P = 95%	Pietila 2009	7.7	3.7	3.5%	7.70 [0.45, 14.95]	-
Wilson 2015 36.1 3.8 3.5% 36.10 [28.65, 43.55] Subtotal (95% CI) 23.2% 23.75 [15.28, 32.22] Heterogeneity: Tau ² = 99.05; Ch ² = 30.67, df = 6 (P < 0.0001); P = 80% 1.2.2 No Craniopharyngioma Gan 2015 32.5 3.6 3.5% 32.50 [25.44, 39.56] Meacham 2005 15 1.2 3.6% 15.00 [12.65, 17.35] Schulte 2010 18.5 5.3 3.4% 18.50 [8.11, 28.89] Shaltin 2011 7 2.4 3.5% 7.00 [23.01, 17.0] Subtotal (95% CI) 1 3.3% 17.86 [8.97, 26.75] Heterogeneity: Tau ² = 71.32; Ch ² = 35.17, df = 3 (P < 0.00001); P = 91% 1.2.3 Craniopharyngioma Amayli 2017 23.3 9.6 2.9% 33.30 [14.48, 52.12] Crom 2010 23.5 5.9 3.3% 23.50 [11.94, 35.06] de Vile 1996 58.7 6.2 3.3% 58.70 [46.55, 70.85] Gautier 2012 44.3 6.4 3.3% 44.30 [31.76, 56.84] Holmer 2009 50 7.7 3.1% 50.00 [34.91, 65.09] Holmer 2009 50 7.7 3.1% 50.00 [19.56, 88.64] Kim 2010 72.7 13.4 2.5% 72.70 [46.44, 98.96] Koutourousiou 2013 43.8 12.4 2.6% 43.80 [29.19, 57.81] Muller 2001 57.3 3.6 3.5% 57.30 [50.24, 64.36] Holmer 2003 53.3 6.4 3.3% 53.30 [02.78, 65.84] Pedreira 2006 50 11.8 2.7% 50.00 [26.87, 73.13] Q1 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Rath 2013 50 15.8 2.2% 50.00 [19.03, 80.97] Willani 1997 77.3 8.9 3.0% 77.30 [59.86, 94.74] Vinchor 2009 70.5 6.9 3.2% 70.50 [58.68, 04.8] Willer 2013 50 15.8 2.2% 50.30 [28.08, 04.74] Winder 203a 53.3 12.9 2.5% 53.30 [82.08, 100.00] Sorva 1988 58 11.3 2.7% 58.00 [26.87, 73.13] Q1 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Rath 2013 50 15.8 2.2% 50.30 [20.27, 85.8] Willani 1997 77.3 8.9 3.0% 77.30 [59.86, 94.74] Vinchor 2009 70.5 6.9 3.2% 70.50 [58.98, 84.02] Heterogeneity: Tau ² = 153.35; Ch ² = 77.85, df = 20 (P < 0.00001); P = 74% Test for overall effect: Z = 16.52 (P < 0.00001) Total (95% CI) 100.0% 42.44 [34.96, 49.92] Heterogeneity: Tau ² = 405.88; Ch ² = 590.52, df = 31 (P < 0.00001); P = 95%	Warner 2014	22.6	3.4	3.5%	22.60 [15.94, 29.26]	
Subtotal (95% CI) 23.2% 23.75 [15.28, 32.22] Heterogeneity: Tau ² = 99.05; Ch ² = 30.67, df = 6 (P < 0.0001); I ² = 80% 1.2.2 No Craniopharyngioma Gan 2015 32.5 3.6 3.5% 32.50 [25.44, 39.56] Meacham 2005 15 1.2 3.6% 15.00 [12.65, 17.35] Meacham 2005 15 1.2 3.6% 15.00 [23.0, 11.70] Shallin 2011 7 2.4 3.5% 7.00 [2.30, 11.70] Subtotal (95% CI) 13.9% 17.88 [8.97, 26.75] Heterogeneity: Tau ² = 71.32; Ch ² = 35.17, df = 3 (P < 0.00001); I ² = 91% 1.2.3 Craniopharyngioma Amayiri 2017 33.3 9.6 2.9% 33.30 [14.48, 52.12] Crom 2010 23.5 5.9 3.3% 58.70 [46.55, 70.85] de Vile 1996 58.7 6.2 3.3% 58.70 [46.55, 70.85] Gautier 2012 44.3 6.4 3.3% 43.00 [31.76, 56.84] Halliogu 2016 53.3 7.4 3.2% 53.30 [38.80, 67.80] Khan 2014 72 9 3.0% 72.00 [54.36, 89.64] Kim 2010 72.7 13.4 2.5% 72.70 [64.44, 99.96] Khan 2014 72 9 3.0% 72.00 [54.36, 89.64] Kim 2010 57.3 3.6 3.5% 57.30 [50.24, 64.36] Muller 2003a 53.3 6.4 3.3% 63.30 [40.76, 65.84] Park 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Rath 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Rath 2013 60.1 18. 2.7% 50.00 [26.37, 73.13] Qi 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Rath 2013 50 15.8 2.2% 50.00 [19.03, 80.97] Sahakitungruang 2011 83.3 10.8 2.8% 63.30 [26.21, 31.00.00] Sorva 1988 58 11.3 2.7% 50.00 [26.87, 73.13] Qi 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Rath 2013 50 15.8 2.2% 50.00 [19.03, 80.97] Sahakitungruang 2011 83.3 10.8 2.8% 53.30 [28.2, 78.58] Villan 1997 77.3 8.9 3.0% 77.30 [59.86, 94.74] Vinchon 2009 70.5 6.9 3.2% 70.50 [58.88, 40.2] Subtotal [95% CI) 100.0% 42.44 [34.96, 49.92] Heterogeneity: Tau ² = 153.35; Ch ² = 77.85, df = 20 (P < 0.00001); I ² = 74% Test for overall effect: Z = 16.52 (P < 0.00001)	Wilson 2015	36.1	3.8	3.5%	36.10 [28.65, 43.55]	
Heterogeneity: Tau ² = 99.05; Chi ² = 30.67, df = 6 (P < 0.0001); l ² = 80% 1.2.2 No Craniopharyngioma Gan 2015 32.5 3.6 3.5% 32.50 [25.44, 39.56] Meacham 2005 15 1.2 3.6% 15.00 [12.65, 17.35] Schulte 2010 18.5 5.3 3.4% 18.50 [8.11, 28.89] Shallin 2011 7 2.4 3.5% 7.00 [23.0, 11.70] Subtotal (95% CI) 13.9% 17.88 [8.97, 26.75] Heterogeneity: Tau ² = 71.32; Chl ² = 35.17, df = 3 (P < 0.00001); l ² = 91% 1.2.3 Craniopharyngioma Armayii 2017 33.3 9.6 2.9% 33.30 [14.48, 52.12] Crom 2010 23.5 5.9 3.3% 23.50 [11.94, 35.06] de Vile 1996 58.7 6.2 3.3% 58.70 [46.55, 70.85] Heitrogeneity: Tau ² = 71.32; Chl ² = 35.77, df = 3 (P < 0.00001); l ² = 91% 1.2.3 Craniopharyngioma Armayii 2017 33.3 9.6 2.9% 33.30 [14.48, 52.12] Crom 2010 23.5 5.9 3.3% 23.50 [11.94, 35.06] de Vile 1996 58.7 6.2 3.3% 58.70 [46.55, 70.85] Hallioglu 2016 53.3 7.4 3.2% 53.30 [38.80, 67.80] Holmer 2009 50 7.7 3.1% 50.00 [34.91, 65.08] Holmer 2009 50 7.7 3.1% 50.00 [24.94, 68.896] Kim 2010 72.7 13.4 2.5% 72.70 [46.44, 98.96] Kim 2010 72.7 13.4 2.5% 72.70 [46.44, 98.96] Holmer 2003a 53.3 6.4 3.3% 37.90 [25.36, 50.44] Park 2013 43.8 12.4 2.6% 43.80 [19.50, 68.10] Lek 2010 43.5 7.3 3.2% 43.50 [29.19, 57.81] Mulier 2003a 53.3 6.4 3.3% 37.90 [25.36, 50.44] Park 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Rath 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Willani 1997 77.3 8.9 3.0% 77.30 [59.86, 94.74] Vinchon 2009 70.5 6.9 3.2% 70.50 [69.8, 84.02] Willani 1997 77.3 8.9 3.0% 77.30 [59.86, 94.74] Vinchon 2009 70.5 6.9 3.2% 70.50 [69.8, 84.02] Heterogeneity: Tau ² = 153.35; Chl ² = 77.85, df = 20 (P < 0.00001); l ² = 74% Test for overall effect: Z = 16.52 (P < 0.00001); l ² = 95%	Subtotal (95% CI)			23.2%	23.75 [15.28, 32.22]	◆
1.2.2 No Craniopharyngioma Gan 2015 32.5 3.6 3.5% 32.50 $[25.44, 39.56]$ Meacham 2005 15 1.2 3.6% 15.00 $[12.65, 17.35]$ Schulte 2010 18.5 5.3 3.4% 18.50 $[11, 28.69]$ Shalitin 2011 7 2.4 3.5% 7.00 $[20.011.70]$ Subtotal (95% CI) 13.9% 17.86 $[8.97, 26.75]$ Heterogeneity: Tau ² = 71.32; Chi ² = 35.17, df = 3 (P < 0.00001); l ² = 91% 1.2.3 Craniopharyngioma Amayiri 2017 33.3 9.6 2.9% 33.30 $[14.48, 52.12]$ Crom 2010 23.5 5.9 3.3% 23.50 $[15.65, 70.85]$ Gautier 2012 44.3 6.4 3.3% 44.30 $[19.50, 67.08]$ Halilogu 2016 53.3 7.4 2.5% 57.30 50.04 $[4.48, 98.96]$ Kuatourousiou 2013 43.8 12.4 2.6% 43.80 $[19.50, 68.10]$ $4.3.5\%$ 57.30 50.24 44.30 77.20 $64.4.98.96]$	Heterogeneity: Tau ² = 99	.05; Chi ² = 30.6	7. df =	6 (P < 0.0	0001); l² = 80%	
1.2.2 No Craniopharyngioma Gan 2015 32.5 3.6 3.5% 32.50 [25.44, 39.56] Meacham 2005 15 1.2 3.6% 15.00 [12.65, 17.35] Schulte 2010 18.5 5.3 3.4% 18.50 [8.11, 28.89] Shalitin 2011 7 2.4 3.5% 7.00 [2.0, 11.70] Subtotal (95% CI) 13.9% 17.86 [8.97, 26.75] Heterogeneity: Tau ² = 71.32; Chi ² = 35.17, df = 3 (P < 0.00001); I ² = 91% Image: State 2012 Amayiri 2017 33.3 9.6 2.9% 33.30 [14.48, 52.12] Crom 2010 23.5 5.9 3.3% 23.50 [11.94, 35.06] Ge Vile 1996 58.7 6.6 4.3 0[31.76, 56.84] Image: 20.2 (1.9, 57.81] Hallioglu 2016 53.3 7.4 3.2% 53.30 [38.80, 67.80] Holmer 2009 50 7.7 3.1% 50.00 [36.96.44] 98.964] Kim 2010 72.7 13.4 2.5% 72.00 [46.49, 89.96] Image: 20.24.64.36] Image: 20.24.64.36] Muller 2001 57.3 3.2% 43.50 [29.19, 57.81] Image: 20.24.64.36] Image: 20.24.64.36]						
Gan 2015 32.5 3.6 3.5% 32.50 [25.44, 39.56] Meacham 2005 15 1.2 3.6% 15.00 [12.65, 17.35] Schulte 2010 18.5 5.3 3.4% 18.50 [8.11, 28.89] Shalifin 2011 7 2.4 3.5% 7.00 [2.30, 11.70] Subtotal (95% CI) 13.9% 77.86 [8.97, 26.75] Heterogeneity: Tau ² = 71.32; Chi ² = 35.17, df = 3 (P < 0.00001); l ² = 91% 1.2.3 Craniopharyngioma Amayiri 2017 33.3 9.6 2.9% 33.30 [14.48, 52.12] Crom 2010 23.5 5.9 3.3% 23.50 [11.94, 35.06] de Vile 1996 58.7 6.2 3.3% 58.70 [46.55, 70.85] Gautier 2012 44.3 6.4 3.3% 44.30 [31.76, 56.84] Haliloglu 2016 53.3 7.4 3.2% 53.30 [38.80, 67.80] Holmer 2009 50 7.7 3.1% 50.00 [34.91, 65.09] Khan 2014 72 9 3.0% 72.00 [54.36, 89.64] Kuin 2010 72.7 13.4 2.5% 72.70 [46.44, 98.96] Koutourousiou 2013 43.8 12.4 2.6% 43.80 [19.50, 68.10] Lek 2010 43.5 7.3 3.6 3.5% 57.30 [50.24, 64.36] Muller 2003a 53.3 6.4 3.3% 53.30 [40.76, 65.84] Pedreira 2006 50 11.8 2.7% 50.00 [26.87, 73.13] Qi 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Sahakitrungruang 2011 83.3 10.8 2.2% 53.30 [38.58, 80.15] Srinivasan 2004 53.3 12.9 2.5% 53.30 [38.62, 74.92] Subtotal (95% CI) 6.9 3.2% 77.30 [59.86, 94.74] Vilichon 2009 70.5 6.9 3.2% 70.50 [56.98, 84.02] Vilichon 2009 70.5 6.9 3.2% 51.30 [38.62, 78.58] Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); l ² = 95% Heterogeneity: Tau ² = 405.88; Chi ² = 590.52, df = 31 (P < 0.00001); l ² = 95%	1.2.2 No Craniopharyng	ioma				
Meacham 2005 15 1.2 3.6% 15.00 [12.65, 17.35] Schulte 2010 18.5 5.3 3.4% 18.50 [8.11, 28.89] Shalitin 2011 7 2.4 3.5% 7.00 [2.30, 11.70] Subtotal (95% CI) 13.9% 17.86 [8.97, 26.75] Heterogeneity: Tau ² = 71.32; Chi ² = 35.17, df = 3 (P < 0.00001); i ² = 91% 1.2.3 Craniopharyngioma Amayiri 2017 33.3 9.6 2.9% 33.30 [14.48, 52.12] Crom 2010 23.5 5.9 3.3% 23.50 [11.94, 35.06] Gautier 2012 44.3 6.4 3.3% 58.70 [64.55, 70.85] Gautier 2012 44.3 6.4 3.3% 50.00 [34.91, 65.09] Kim 2010 72.7 13.4 2.5% 72.70 [46.44, 98.96] Koutourousiou 2013 43.8 12.4 2.6% 43.80 [29.19, 57.81] Muller 2001 43.5 7.3 3.5 53.20 [40.76, 65.84] Park 2013 37.9 6.4 3.3% 37.90 [25.36, 50.44] Park 2013 50 15.8 2.7% 50.00 [26.87, 73.13] Gi 2013 66.1 8.	Gan 2015	32.5	3.6	3.5%	32.50 [25.44, 39.56]	-
Schulte 2010 18.5 5.3 3.4% 18.50 [8.11, 28.89] Shalitin 2011 7 2.4 3.5% 7.00 [2.30, 11.70] 13.9% 17.86 [8.97, 26.75] Heterogeneity: Tau ² = 71.32; Chi ² = 35.17, df = 3 (P < 0.00001); I ² = 91% 1.2.3 Craniopharyngioma Amayin 2017 33.3 9.6 2.9% 33.30 [14.48, 52.12] Crom 2010 23.5 5.9 3.3% 23.50 [11.94, 35.06] de Vie 1996 58.7 6.2 3.3% 58.70 [46.55, 70.85] Gautier 2012 44.3 6.4 3.3% 44.30 [31.76, 56.84] Haliloglu 2016 53.3 7.4 3.2% 53.30 [38.80, 67.80] Holmer 2009 50 7.7 3.1% 50.00 [34.91, 65.09] Koutourousiou 2013 43.8 12.4 2.5% 72.00 [64.36, 89.64] Kim 2010 72.7 13.4 2.5% 72.00 [64.36, 89.64] Muller 2001 57.3 3.6 3.5% 57.30 [29.19, 57.81] Muller 2001 57.3 3.6 4 3.3% 55.30 [40.76, 65.84] Pedreira 2006 50 11.8 2.7% 50.00 [28.87, 73.13] Gi 2013 66.1 14.5 3.4% 66.10 [57.28, 74.92] Rath 2013 50 15.8 2.2% 50.00 [28.87, 73.13] Gi 2013 50 15.8 2.2% 50.00 [19.03, 80.97] Sahakitrungruang 2011 83.3 10.8 2.8% 83.30 [62.13, 100.00] Sorva 1988 51 11.3 2.7% 58.00 [28.67, 73.13] Gi 2013 50 15.8 2.2% 50.00 [19.03, 80.97] Sahakitrungruang 2011 83.3 10.8 2.8% 83.30 [62.13, 100.00] 50 rist.8 2.2% 50.00 [19.03, 80.97] Sahakitrungruang 2011 83.3 12.9 2.5% 53.30 [28.02, 78.58] Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); I ² = 74% Test for overall effect: Z = 16.52 (P < 0.00001) Total (95% CI) Heterogeneity: Tau ² = 405.88; Chi ² = 590.52, df = 31 (P < 0.00001); I ² = 95%	Meacham 2005	15	1.2	3.6%	15.00 [12.65, 17.35]	•
Shalifu 2011 7 2.4 3.5% 7.00 [2.30, 11.70] Subtotal (95% CI) 13.9% 17.86 [8.97, 26.75] Heterogeneity: Tau ² = 71.32; Chi ² = 35.17, df = 3 (P < 0.00001); P = 91%	Schulte 2010	18.5	5.3	3.4%	18.50 [8.11, 28.89]	
Subtotal (95% CI) 13.9% 17.86 [8.97, 26.75] Heterogeneitly: Tau ² = 71.32; Chi ² = 35.17, df = 3 (P < 0.00001); l ² = 91% 1.2.3 Craniopharyngioma Amayiri 2017 33.3 9.6 2.9% 33.30 [14.48, 52.12] Crom 2010 23.5 5.9 3.3% 23.50 [11.94, 35.06] de Vile 1996 58.7 6.2 3.3% 58.70 [46.55, 70.85] Gautier 2012 44.3 6.4 3.3% 44.30 [31.76, 56.84] Haliloglu 2016 53.3 7.4 3.2% 53.30 [38.80, 67.80] Holmer 2009 50 7.7 3.1% 50.00 [34.91, 65.09] Khan 2014 72 9 3.0% 72.70 [46.44, 99.66] Koutourousiou 2013 43.8 12.4 2.6% 43.80 [19.50, 68.10] Lek 2010 72.7 13.4 2.5% 57.30 [50.24, 64.36] Muller 2003a 53.3 6.4 3.3% 57.30 [50.24, 64.36] Muller 2003a 53.3 6.4 3.3% 53.30 [40.76, 65.84] Park 2013 37.9 6.4 3.3% 53.30 [28.07, 76, 65.84] Park 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Rath 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Rath 2013 60.1 1.8 2.7% 50.00 [26.87, 73.13] Gi 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Rath 2013 50 15.8 2.2% 50.00 [19.03, 80.97] Sanakitrungruang 2011 83.3 10.8 2.8% 83.30 [62.13, 100.00] Sorva 1988 58 11.3 2.7% 58.00 [35.85, 80.15] Srinlwasan 2004 53.3 12.9 2.5% 53.30 [28.02, 78.58] Villani 1997 77.73 8.9 3.0% 77.30 [59.86, 94.74] Vinchon 2009 70.5 6.9 3.2% 70.50 [56.98, 84.02] Subtotal (95% CI) 62.9% 54.40 [47.95, 60.86] Heterogeneity: Tau ² = 165.32 (P < 0.00001); l ² = 74% Test for overall effect: Z = 16.52 (P < 0.00001); l ² = 95%	Shalitin 2011	7	2.4	3.5%	7.00 [2.30, 11.70]	+
Heterogeneilty: Tau ² = 71.32; Chi ² = 35.17, df = 3 (P < 0.00001); l ² = 91% 1.2.3 Craniopharyngioma Amayiri 2017 33.3 9.6 2.9% 33.30 [14.48, 52.12] Crom 2010 23.5 5.9 3.3% 23.50 [11.94, 35.06] de Vile 1996 58.7 6.2 3.3% 58.70 [46.55, 70.85] Gautier 2012 44.3 6.4 3.3% 44.30 [31.76, 56.84] Hallioglu 2016 53.3 7.4 3.2% 53.30 [38.80, 67.80] Holmer 2009 50 7.7 3.1% 50.00 [34.91, 65.09] Khan 2014 72 9 3.0% 72.00 [54.36, 89.64] Kim 2010 72.7 13.4 2.5% 72.70 [46.44, 98.96] Koutourousiou 2013 43.8 12.4 2.6% 43.80 [19.50, 68.10] Lek 2010 43.5 7.3 3.2% 43.50 [29.19, 57.81] Muller 2003a 53.3 6.4 3.3% 53.30 [40.76, 65.84] Park 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Gi 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Gi 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Rath 2013 50 15.8 2.2% 50.00 [19.03, 80.97] Sahakitrungruang 2011 83.3 10.8 2.8% 83.30 [62.13, 100.00] Sorva 1988 58 11.3 2.7% 58.00 [35.85, 80.15] Srinivasan 2004 53.3 12.9 2.5% 53.30 [28.02, 78.58] Villani 1997 77.3 8.9 3.0% 77.30 [59.86, 84.02] Subtotal (95% Cl) 62.9% 54.40 [47.95, 60.86] Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); l ² = 74% Test for overall effect: Z = 16.52 (P < 0.00001) Total (95% Cl) 100.0% 42.44 [34.96, 49.92] Heterogeneity: Tau ² = 405.88; Chi ² = 590.52, df = 31 (P < 0.00001); l ² = 95%	Subtotal (95% CI)			13.9%	17.86 [8.97, 26.75]	•
1.2.3 Craniopharyngioma Amayiri 2017 33.3 9.6 2.9% 33.30 $[14.48, 52.12]$ Crom 2010 23.5 5.9 3.3% 58.70 $[46.55, 70.85]$ Gautier 2012 44.3 6.4 3.3% 58.70 $[46.55, 70.85]$ Gautier 2012 44.3 6.4 3.3% 58.70 $[46.55, 70.85]$ Gautier 2012 44.3 6.4 3.3% 44.30 $[31.76, 56.84]$ Hailioglu 2016 53.3 7.4 3.2% 53.30 $38.80, 67.80]$ Hoimer 2009 50 7.7 3.1% 50.00 $[34.91, 65.09]$ Khan 2014 72.9 $9.3.0\%$ 72.00 $[46.44, 98.96]$ $$	Heterogeneity: Tau ² = 71.	.32; Chi ² = 35.1	7, df =	3 (P < 0.0	00001); l² = 91%	
1.2.3 Craniopharyngioma Amayiri 2017 33.3 9.6 2.9% 33.30 [14.48, 52.12] Crom 2010 23.5 5.9 3.3% 23.50 [11.94, 35.06] de Vile 1996 58.7 6.2 3.3% 58.70 [46.55, 70.85] Gautier 2012 44.3 6.4 3.3% 44.30 [31.76, 56.84] Hallioglu 2016 53.3 7.4 3.2% 53.30 [38.80, 67.80] Hoimer 2009 50 7.7 3.1% 50.00 [34.91, 65.09] Kim 2010 72.7 13.4 2.5% 72.70 [46.44, 98.96] Koutourousiou 2013 43.8 12.4 2.6% 43.80 [19.50, 68.10] Lek 2010 43.5 7.3 3.2% 43.50 [29.19, 57.81] Muller 2001 57.3 3.6 3.5% 57.30 [50.24, 64.36]						
Amayiri 201733.39.62.9%33.30 $[14.48, 52.12]$ Crom 201023.55.93.3%23.50 $[11.94, 35.06]$ de Vile 199658.76.23.3%58.70 $[46.55, 70.85]$ Gautier 201244.36.43.3%44.30 $[31.76, 56.84]$ Haliloglu 201653.37.43.2%53.30 $[38.80, 67.80]$ Holmer 2009507.73.1%50.00 $[34.91, 65.09]$ Khan 20147293.0%72.00 $[54.36, 89.64]$ Kim 201072.713.42.5%72.70 $[46.44, 98.96]$ Koutourousiou 201343.812.42.6%43.80 $[19.50, 68.10]$ Lek 201043.57.33.2%43.50 $[29.19, 57.81]$ Muller 2003a53.36.43.3%37.90 $[25.36, 50.44]$ Pedreira 20065011.82.7%50.00 $[19.03, 80.97]$ Sahakitrungruang 201183.310.82.8%83.30 $[26.21, 3, 100.00]$ Sorva 19885811.32.7%58.00 $[35.85, 80.15]$ Sirnivasan 200453.312.92.5%53.30 $[28.02, 78.58]$ Villani 199777.38.93.0%77.30 $[59.86, 94.74]$ Vinchon 200970.56.93.2%70.50 $[56.98, 84.02]$ Subtotal (95% CI)62.9%54.40 [47.95, 60.86]Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); i ² = 74%Heterogeneity: Tau ² = 405.8	1.2.3 Craniopharyngiom	a				
Crom 2010 23.5 5.9 3.3% 23.50 [11.94, 35.06] de Vile 1996 58.7 6.2 3.3% 58.70 [46.55, 70.85] Gautier 2012 44.3 6.4 3.3% 44.30 [31.76, 56.84] Hallioglu 2016 53.3 7.4 3.2% 53.30 [38.80, 67.80] Holmer 2009 50 7.7 3.1% 50.00 [34.91, 65.09] Kim 2014 72 9 3.0% 72.00 [54.36, 89.64] Kim 2010 72.7 13.4 2.5% 72.70 [46.44, 98.96] Koutourousiou 2013 43.8 12.4 2.6% 43.50 [29.19, 57.81] Muller 2001 43.5 7.3 3.2% 43.50 [29.19, 57.81] Muller 2003a 53.3 6.4 3.3% 53.30 [50.24, 64.36] Park 2013 37.9 6.4 3.3% 53.00 [26.87, 73.13] Qi 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Rath 2013 50 15.8 2.2% 50.00 [26.87, 73.13] Sorva 1988 58 11.3 2.7% 58.00 [35.85, 80.015] Strinivasan 2004 53.3 <	Amayiri 2017	33.3	9.6	2.9%	33.30 [14.48, 52.12]	_
de Vile 1996 58.7 6.2 3.3% 58.70 [46.55, 70.85] Gautier 2012 44.3 6.4 3.3% 44.30 [31.76, 56.84] Haliloglu 2016 53.3 7.4 3.2% 53.30 [38.80, 67.80] Holmer 2009 50 7.7 3.1% 50.00 [34.91, 65.09] Khan 2014 72 9 3.0% 72.00 [54.36, 89.64] Kim 2010 72.7 13.4 2.5% 72.70 [46.44, 98.96] Koutourousiou 2013 43.8 12.4 2.6% 43.80 [19.50, 68.10] Lek 2010 43.5 7.3 3.2% 43.50 [29.19, 57.81] Muller 2001 57.3 3.6 3.5% 57.30 [50.24, 64.36] Muller 2003a 53.3 6.4 3.3% 53.30 [40.76, 65.84] Park 2013 37.9 6.4 3.3% 37.90 [25.36, 50.44] Pedrelira 2006 50 11.8 2.7% 50.00 [26.87, 73.13] Qi 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Rath 2013 50 15.8 2.2% 50.00 [19.03, 80.97] Sahakitrungruang 2011 83.3 10.8 2.8% 83.30 [28.02, 78.58] Villani 1997 77.3 8.9 3.0% 77.30 [59.86, 94.74] Vinchon 2009 70.5 6.9 3.2% 70.05 [56.98, 84.02] Subtotal (95% CI) 62.9% 54.40 [47.95, 60.86] Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); I ² = 74% Test for overall effect: Z = 16.52 (P < 0.00001) Total (95% CI) 100.0% 42.44 [34.96, 49.92] Heterogeneity: Tau ² = 405.88; Chi ² = 590.52, df = 31 (P < 0.00001); I ² = 95%	Crom 2010	23.5	5.9	3.3%	23.50 [11.94, 35.06]	
Gautier 201244.36.43.3%44.30 $[31.76, 56.84]$ Haliloglu 201653.37.43.2%53.30 $[38.80, 67.80]$ Holmer 2009507.73.1%50.00 $[34.91, 65.09]$ Khan 20147293.0%72.00 $[54.36, 89.64]$ Kim 201072.713.42.5%72.70 $[46.44, 98.96]$ Koutourousiou 201343.812.42.6%43.80 $[19.50, 68.10]$ Lek 201043.57.33.2%43.50 $[29.19, 57.81]$ Muller 200157.33.63.5%57.30 $[50.24, 64.36]$ Park 201350.36.43.3%37.90 $[25.36, 50.44]$ Pedreira 20065011.82.7% 50.00 $[26.87, 73.13]$ Qi 201366.14.53.4%66.10 $[57.28, 74.92]$ Rath 20135015.82.2% 50.00 $[19.03, 80.97]$ Sahakitrungruang 201183.310.82.8% 83.30 $[62.13, 100.00]$ Sorva 19885811.32.7% 58.00 $[36.86, 94.74]$ Villani 199777.38.93.0%77.50 $[56.98, 84.02]$ Subtotal (95% CI)62.9%54.40 [47.95, 60.86]Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); I ² = 74%Test for overall effect: Z = 16.52 (P < 0.00001)	de Vile 1996	58.7	6.2	3.3%	58.70 [46.55, 70.85]	_ . _
Haliloglu 201653.37.43.2%53.3053.80, 67.80Holmer 2009507.73.1%50.00[34.91, 65.09]Khan 20147293.0%72.00[54.36, 89.64]Kim 201072.713.42.5%72.70[46.44, 98.96]Koutourousiou 201343.812.42.6%43.80[19.50, 68.10]Lek 201043.57.33.2%43.50[29.19, 57.81]Muller 200157.33.63.5%57.30[50.24, 64.36]Muller 2003a53.36.43.3%53.30[40.76, 65.84]Pedreira 20065011.82.7%50.00[26.87, 73.13]Qi 201366.14.53.4%66.10[57.28, 74.92]Rath 20135015.82.2%50.00[19.03, 80.97]Sahakitrungruang 201183.310.82.8%83.30[62.13, 100.00]Sorva 19885811.32.7%58.00[56.98, 84.02]Sinivasan 200453.312.92.5%53.00[59.86, 94.74]Vinchon 200970.56.93.2%70.50[56.98, 84.02]Subtotal (95% CI)62.9%54.40 [47.95, 60.86]Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); I ² = 74%Test for overall effect: Z = 16.52 (P < 0.00001)	Gautier 2012	44.3	6.4	3.3%	44.30 [31.76, 56.84]	
Holmer 2009507.73.1% 50.00 [34.91, 65.09]Khan 2014729 3.0% 72.00 [54.36, 89.64]Kim 201072.7 13.4 2.5% 72.70 [46.44, 98.96]Koutourousiou 201343.8 12.4 2.6% 43.80 [19.50, 68.10]Lek 201043.5 7.3 3.2% 43.50 [29.19, 57.81]Muller 200157.3 3.6 3.5% 57.30 [50.24, 64.36]Muller 2003a53.3 6.4 3.3% 53.30 [40.76, 65.84]Park 201337.9 6.4 3.3% 57.30 [26.87, 73.13]Qi 201366.1 4.5 3.4% 66.10 [57.28, 74.92]Rath 201350 15.8 2.2% 50.00 [26.87, 73.13]Sahakitrungruang 2011 83.3 10.8 2.8% 83.30 [62.13, 100.00]Sorva 198858 11.3 2.7% 58.00 [35.85, 80.15]Srinivasan 2004 53.3 12.9 2.5% 53.00 [28.02, 78.58]Villani 1997 77.3 8.9 3.0% 77.30 [59.86, 94.74]Vinchon 2009 70.5 6.9 3.2% 70.50 [56.98, 84.02]Subtotal (95% CI) 100.0% 42.44 [34.96, 49.92]Heterogeneity: Tau ² = 16.52 (P < 0.00001)	Haliloglu 2016	53.3	7.4	3.2%	53.30 [38.80, 67.80]	
Khan 2014729 3.0% 72.00 $[54.36, 89.64]$ Kim 201072.7 13.4 2.5% 72.70 $[46.44, 98.96]$ Koutourousiou 2013 43.8 12.4 2.6% 43.80 $[19.50, 68.10]$ Lek 2010 43.5 7.3 3.2% 43.50 $[29.19, 57.81]$ Muller 2001 57.3 3.6 3.5% 57.30 $[50.24, 64.36]$ Muller 2003a 53.3 6.4 3.3% 53.30 $[40.76, 65.84]$ Park 2013 37.9 6.4 3.3% 53.30 $[40.76, 65.84]$ Pedreira 2006 50 11.8 2.7% 50.00 $[26.87, 73.13]$ Qi 2013 66.1 4.5 3.4% 66.10 $[57.28, 74.92]$ Rath 2013 50 15.8 2.2% 50.00 $[19.03, 80.97]$ Sahakitrungruang 2011 83.3 10.8 2.8% 83.30 $[62.13, 100.00]$ Sorva 1988 58 11.3 2.7% 58.00 $[35.85, 80.15]$ Villani 1997 77.3 8.9 3.0% 77.30 $[59.86, 94.74]$ Vinchon 2009 70.5 6.9 3.2% 70.50 $[56.98, 84.02]$ Subtotal (95% Cl) 62.9% 54.40 $[47.95, 60.86]$ Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 $(P < 0.00001); I2 = 74\%$ Total (95% Cl) 100.0% 42.44 $[34.96, 49.92]$ Heterogeneity: Tau ² = 405.88; Chi ² = 590.52, df = 31 $(P < 0.00001); I2 = 95\%$	Holmer 2009	50	7.7	3.1%	50.00 [34.91, 65.09]	_ -
Kim 201072.713.42.5%72.70[46.44, 98.96]Koutourousiou 201343.812.42.6%43.80[19.50, 68.10]Lek 201043.57.33.2%43.50[29.19, 57.81]Muller 200157.33.63.5%57.30[50.24, 64.36]Muller 2003a53.36.43.3%53.30[40.76, 65.84]Park 201337.96.43.3%57.90[25.36, 50.44]Pedreira 20065011.82.7%50.00[26.87, 73.13]Qi 201366.14.53.4%66.10[57.28, 74.92]Rath 20135015.82.2%50.00[19.03, 80.97]Sahakitrungruang 201183.310.82.8%83.30[62.13, 100.00]Sorva 19885811.32.7%58.00[35.85, 80.15]Srinivasan 200453.312.92.5%53.30[28.02, 78.56]Villani 199777.38.93.0%77.30[59.86, 94.74]Vinchon 200970.56.93.2%70.50[56.98, 84.02]Subtotal (95% Cl)62.9%54.40[47.95, 60.86]Heterogeneily: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); l ² = 74%Total (95% Cl)100.0%42.44[34.96, 49.92]Heterogeneity: Tau ² = 405.88; Chi ² = 590.52, df = 31 (P < 0.00001); l ² = 95%5010	Khan 2014	72	9	3.0%	72.00 [54.36, 89.64]	_ _
Koutourousiou 2013 43.8 12.4 2.6% 43.80 [19.50, 68.10] Lek 2010 43.5 7.3 3.2% 43.50 [29.19, 57.81] Muller 2001 57.3 3.6 3.5% 57.30 [50.24, 64.36] Muller 2003a 53.3 6.4 3.3% 53.30 [40.76, 65.84] Park 2013 37.9 6.4 3.3% 57.00 [25.36, 50.44] Pedreira 2006 50 11.8 2.7% 50.00 [26.87, 73.13] Qi 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Rath 2013 50 15.8 2.2% 50.00 [19.03, 80.97] Sahakitrungruang 2011 83.3 10.8 2.8% 83.30 [62.13, 100.00] Sorva 1988 58 11.3 2.7% 58.00 [35.85, 80.15] Srinivasan 2004 53.3 12.9 2.5% 53.30 [28.02, 78.58] Villani 1997 77.3 8.9 3.0% 77.30 [59.86, 94.74] Vinchon 2009 70.5 6.9 3.2% 70.50 [56.98, 84.02] Subtotal (95% Cl) 62.9% 54.40 [47.95, 60.86] 44.44 Heterogeneity: Tau ² = 153.35; Chi	Kim 2010	72.7	13.4	2.5%	72.70 [46.44, 98.96]	
Lek 201043.57.33.2%43.50 $[29.19, 57.81]$ Muller 200157.33.63.5% 57.30 $[50.24, 64.36]$ Muller 2003a53.36.43.3% 53.30 $[40.76, 65.84]$ Park 201337.96.43.3% 57.90 $[25.36, 50.44]$ Pedreira 20065011.82.7% 50.00 $[26.87, 73.13]$ Qi 201366.14.53.4%66.10 $[57.28, 74.92]$ Rath 20135015.82.2% 50.00 $[19.03, 80.97]$ Sahakitrungruang 201183.310.82.8% 83.30 $[62.13, 100.00]$ Sorva 19885811.32.7% 58.00 $[35.85, 80.15]$ Srinivasan 200453.312.92.5% 53.30 $[28.02, 78.58]$ Villani 199777.38.9 3.0% 77.30 $[59.86, 94.74]$ Vinchon 200970.5 6.9 3.2% 70.50 $[56.98, 84.02]$ Subtotal (95% CI)62.9%54.40 [47.95, 60.86]Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); I ² = 74%Total (95% CI)100.0% 42.44 [34.96, 49.92]Heterogeneity: Tau ² = 405.88; Chi ² = 590.52, df = 31 (P < 0.00001); I ² = 95%	Koutourousiou 2013	43.8	12.4	2.6%	43.80 [19.50, 68.10]	_
Muller 200157.33.6 3.5% 57.30 $[50.24, 64.36]$ Muller 2003a53.3 6.4 3.3% 53.30 $[40.76, 65.84]$ Park 2013 37.9 6.4 3.3% 37.90 $[25.36, 50.44]$ Pedreira 2006 50 11.8 2.7% 50.00 $[26.87, 73.13]$ Qi 2013 66.1 4.5 3.4% 66.10 $[57.28, 74.92]$ Rath 2013 50 15.8 2.2% 50.00 $[19.03, 80.97]$ Sahakitrungruang 2011 83.3 10.8 2.8% 83.30 $[62.13, 100.00]$ Sorva 1988 58 11.3 2.7% 58.00 $[35.85, 80.15]$ Srinivasan 2004 53.3 12.9 2.5% 53.30 $[28.02, 78.58]$ Villani 1997 77.3 8.9 3.2% 70.50 $[59.86, 94.74]$ Vinchon 2009 70.5 6.9 3.2% 70.50 $[56.98, 84.02]$ Subtotal (95% CI) 62.9% 54.40 $[47.95, 60.86]$ Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); I ² = 74\% 42.44 $[34.96, 49.92]$ Heterogeneity: Tau ² = 405.88; Chi ² = 590.52, df = 31 (P < 0.00001); I ² = 95\% 40.5% 50.5%	Lek 2010	43.5	7.3	3.2%	43.50 [29.19, 57.81]	_ _
Muller 2003a53.36.43.3%53.30[40.76, 65.84]Park 201337.96.43.3%37.90[25.36, 50.44]Pedreira 20065011.82.7%50.00[26.87, 73.13]Qi 201366.14.53.4%66.10[57.28, 74.92]Rath 20135015.82.2%50.00[19.03, 80.97]Sahakitrungruang 201183.310.82.8%83.30[62.13, 100.00]Sorva 19885811.32.7%58.00[35.85, 80.15]Srinivasan 200453.312.92.5%53.30[28.02, 78.58]Villani 199777.38.93.0%77.30[59.86, 94.74]Vinchon 200970.56.93.2%70.50[56.98, 84.02]Subtotal (95% CI)62.9%54.40 [47.95, 60.86] \bullet Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); I ² = 74% \bullet Total (95% CI)100.0%42.44 [34.96, 49.92]Heterogeneity: Tau ² = 405.88; Chi ² = 590.52, df = 31 (P < 0.00001); I ² = 95% \bullet	Muller 2001	57.3	3.6	3.5%	57.30 [50.24, 64.36]	
Park 2013 37.9 6.4 3.3% 37.90 $[25.36, 50.44]$ Pedreira 2006 50 11.8 2.7% 50.00 $[26.87, 73.13]$ Qi 2013 66.1 4.5 3.4% 66.10 $[57.28, 74.92]$ Rath 2013 50 15.8 2.2% 50.00 $[19.03, 80.97]$ Sahakitrungruang 2011 83.3 10.8 2.8% 83.30 $[62.13, 100.00]$ Sorva 1988 58 11.3 2.7% 58.00 $[35.85, 80.15]$ Srinivasan 2004 53.3 12.9 2.5% 53.30 $[28.02, 78.58]$ Villani 1997 77.3 8.9 3.0% 77.30 $[59.86, 94.74]$ Vinchon 2009 70.5 6.9 3.2% 70.50 $[56.98, 84.02]$ Subtotal (95% CI) 62.9% 54.40 $[47.95, 60.86]$ 4.02 4.02 4.02 4.02 4.02 4.02 4.02 4.02 4.02 4.02 4.02 4.02 4.02 4.02 4.02 4.02 4.02 4.02 4.0	Muller 2003a	53.3	6.4	3.3%	53.30 [40.76, 65.84]	
Pedreira 2006 50 11.8 2.7% 50.00 [26.87, 73.13] Qi 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Rath 2013 50 15.8 2.2% 50.00 [19.03, 80.97] Sahakitrungruang 2011 83.3 10.8 2.8% 83.30 [62.13, 100.00] Sorva 1988 58 11.3 2.7% 58.00 [35.85, 80.15] Srinivasan 2004 53.3 12.9 2.5% 53.30 [28.02, 78.58] Villani 1997 77.3 8.9 3.0% 77.30 [59.86, 94.74] Vinchon 2009 70.5 6.9 3.2% 70.50 [56.98, 84.02] Subtotal (95% CI) 62.9% 54.40 [47.95, 60.86] 4.74 Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); l ² = 74% 4.40 [47.95, 60.86] 4.40 [47.95, 60.86] Test for overall effect: Z = 16.52 (P < 0.00001)	Park 2013	37.9	6.4	3.3%	37.90 [25.36, 50.44]	
Qi 2013 66.1 4.5 3.4% 66.10 [57.28, 74.92] Rath 2013 50 15.8 2.2% 50.00 [19.03, 80.97] Sahakitrungruang 2011 83.3 10.8 2.8% 83.30 [62.13, 100.00] Sorva 1988 58 11.3 2.7% 58.00 [35.85, 80.15] Srinivasan 2004 53.3 12.9 2.5% 53.30 [28.02, 78.58] Villani 1997 77.3 8.9 3.0% 77.30 [59.86, 94.74] Vinchon 2009 70.5 6.9 3.2% 70.50 [56.98, 84.02] Subtotal (95% CI) 62.9% 54.40 [47.95, 60.86] Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); l ² = 74% Test for overall effect: Z = 16.52 (P < 0.00001)	Pedreira 2006	50	11.8	2.7%	50.00 [26.87, 73.13]	_ _
Rath 2013 50 15.8 2.2% 50.00 [19.03, 80.97] Sahakitrungruang 2011 83.3 10.8 2.8% 83.30 [62.13, 100.00] Sorva 1988 58 11.3 2.7% 58.00 [35.85, 80.15] Srinivasan 2004 53.3 12.9 2.5% 53.30 [28.02, 78.58] Villani 1997 77.3 8.9 3.0% 77.30 [59.86, 94.74] Vinchon 2009 70.5 6.9 3.2% 70.50 [56.98, 84.02] Subtotal (95% CI) 62.9% 54.40 [47.95, 60.86] Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); I ² = 74% Test for overall effect: Z = 16.52 (P < 0.00001)	Qi 2013	66.1	4.5	3.4%	66.10 [57.28, 74.92]	
Sahakitrungruang 2011 83.3 10.8 2.8% 83.30 [62.13 , 100.00] Sorva 1988 58 11.3 2.7% 58.00 [35.85 , 80.15] Srinivasan 2004 53.3 12.9 2.5% 53.30 [28.02 , 78.58] Villani 1997 77.3 8.9 3.0% 77.30 [59.86 , 94.74] Vinchon 2009 70.5 6.9 3.2% 70.50 [56.98 , 84.02] Subtotal (95% CI) 62.9% 54.40 [47.95 , 60.86] Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); I ² = 74% Test for overall effect: Z = 16.52 (P < 0.00001)	Rath 2013	50	15.8	2.2%	50.00 [19.03, 80.97]	-
Sorva 1988 58 11.3 2.7% 58.00 [$35.85, 80.15$] Srinivasan 2004 53.3 12.9 2.5% 53.30 [$28.02, 78.58$] Villani 1997 77.3 8.9 3.0% 77.30 [$59.86, 94.74$] Vinchon 2009 70.5 6.9 3.2% 70.50 [$56.98, 84.02$] Subtotal (95% CI) 62.9% 54.40 [$47.95, 60.86$] Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); I ² = 74% Test for overall effect: Z = 16.52 (P < 0.00001)	Sahakitrungruang 2011	83.3	10.8	2.8%	83.30 [62.13, 100.00]	
Srinivasan 2004 53.3 12.9 2.5% 53.30 $[28.02, 78.58]$ Villani 1997 77.3 8.9 3.0% 77.30 $[59.86, 94.74]$ Vinchon 2009 70.5 6.9 3.2% 70.50 $[56.98, 84.02]$ Subtotal (95% CI) 62.9% 54.40 $[47.95, 60.86]$ Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); I ² = 74% Test for overall effect: Z = 16.52 (P < 0.00001)	Sorva 1988	58	11.3	2.7%	58.00 [35.85, 80.15]	
Villani 1997 77.3 8.9 3.0% 77.30 $[59.86, 94.74]$ Vinchon 2009 70.5 6.9 3.2% 70.50 $[56.98, 84.02]$ Subtotal (95% Cl) 62.9% 54.40 $[47.95, 60.86]$ Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); I ² = 74% Test for overall effect: Z = 16.52 (P < 0.00001)	Srinivasan 2004	53.3	12.9	2.5%	53.30 [28.02, 78.58]	_
Vinchon 2009 70.5 6.9 3.2% 70.50 $[56.98, 84.02]$ Subtotal (95% CI) 62.9% 54.40 $[47.95, 60.86]$ Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); I ² = 74% Test for overall effect: Z = 16.52 (P < 0.00001) Total (95% CI) 100.0% 42.44 $[34.96, 49.92]$ Heterogeneity: Tau ² = 405.88; Chi ² = 590.52, df = 31 (P < 0.00001); I ² = 95% 50 100	Villani 1997	77.3	8.9	3.0%	77.30 [59.86, 94.74]	
Subtotal (95% CI) 62.9% 54.40 [47.95, 60.86] Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); I ² = 74% Test for overall effect: Z = 16.52 (P < 0.00001)	Vinchon 2009	70.5	6.9	3.2%	70.50 [56.98, 84.02]	
Heterogeneity: Tau ² = 153.35; Chi ² = 77.85, df = 20 (P < 0.00001); I ² = 74% Test for overall effect: Z = 16.52 (P < 0.00001) Total (95% Cl) 100.0% 42.44 [34.96, 49.92] $+$ Heterogeneity: Tau ² = 405.88; Chi ² = 590.52, df = 31 (P < 0.00001); I ² = 95% 0 50 10	Subtotal (95% CI)			62.9%	54.40 [47.95, 60.86]	•
Test for overall effect: Z = 16.52 (P < 0.00001)	Heterogeneity: Tau ² = 15	3.35; Chi ² = 77.8	85, df	= 20 (P <	0.00001); I* = 74%	
Total (95% CI) 100.0% 42.44 [34.96, 49.92] Heterogeneity: Tau ² = 405.88; Chi ² = 590.52, df = 31 (P < 0.00001); l ² = 95%	Test for overall effect: Z =	: 16.52 (P < 0.0	0001)			
Heterogeneity: Tau ² = 405.88; Chi ² = 590.52, df = 31 (P < 0.00001); l ² = 95%	Total (95% CI)			100.0%	42.44 [34.96, 49.92]	•
	Heterogeneity: Tau ² = 40	5.88; Chi ² = 590).52, d	f = 31 (P ·	< 0.00001); l ² = 95%	6 50 10

Test for overall effect: Z = 11.12 (P < 0.00001) Test for subgroup differences: Chi² = 55.16, df = 2 (P < 0.00001), l² = 96.4%



Wang KW et al. <u>Clin Obes.</u> 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



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Question

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

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OPEN 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. Johnston⁸, Shayna M. Zelcer⁹, Shahrad Rod Rassekh¹⁰, Sarah Burrow¹¹ 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

		Control					
	Total	Male	Female	Total	Male	Female	n-value ^a
Variables	(n=106)	(n=55)	(n=51)	(n=56)	(n=33)	(n=23)	p-value
	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 ^o	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

Predictors of adiposity in children with brain tumors

	%FM		WHR		WHtR		
Variables	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	

Survivors have higher total adiposity vs non-cancer controls





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. Johnston⁵, S. M. Zelcer⁶, S. R. Rassekh⁷, S. Ladhani^{1,2}, A. Socha^{1,2}, J. Shinuda^{1,2}, S. Jaber^{1,2}, S. Burrow⁸, S. K. Singh^{9,10}, L. Banfield¹¹, 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

		SCBT		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
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. Tau#= 0.	DO; Chiª	= 3.86	5, dí = 1	(P = 0.	05); P	= 74%			
Test for overall effect: Z =	= 2.53 (f	P = 0.0	1)						
4.1.2 Waist-to-height ra	itio								
Siviero-Mlachon 2011	0.5	0.05	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	Z3.3%	0.08 (0.06, 0.10)	
Wang 2017	0.47	0.05	56	0.45	0.08	106	Z3.1%	0.02 [-0.00, 0.04]	
Subtotal (95% CI)			154			323	64.2%	0.06 [0.01, 0.10]	-
Heterogeneity Tau*= 0.	00; Chi*	= 15.8	58, df=	2 (P = 0	0.0004); I* = 8	7%		
Test for overall effect: Z =	= 2.60 (f	P = 0.0	09)						
Total (95% CI)			226			438	100.0%	0.06 [0.03, 0.09]	•
Heterogeneity Tau*= 0.	DO; Chi*	= 19.8	31. df=	4 (P = 0	0.0005); I ¥= 8	0%		
Test for overall effect: Z =	= 4.21 (F	<	001)	18.					-0.2 -0.1 0 0.1 0 Non concer controls SORT
Test for subgroup differe	ances: C	2h/* = (0.27. df	= 1 (P =	0.60)	. I* = 09	%		Non-cancer controls SOBT

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Leptin correlates positively with the fat mass in SCBT





natureresearch

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

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Adopted from Sims et al. Scientific Reports, 2020

Adiponectin correlates negatively with the fat mass in SCBT and controls



scientific reports

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

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Adapted from Ronsley et al. Scientific Reports, 2021

Question

• Are there effective interventions to treat obesity now?

obesity reviews

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Obesity Treatment

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

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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



Eligibility/ Rand	lomization						
Recruitment visit	visit	Visit	Visit	Visit	Visit	Visit	Visit
						I	
4-6 Weeks							
4-0 WCCKS	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 Anthropometrics WHR, WHtR BP, PR Assess recruitment numbers and consent, procedure adherence, and completeness of questionnaire collection rates	Questionnaires Interviews/ Focus groups Anthropometrics WHR, WHR BP, PR Assess recruitment numbers and consent, procedure adherence, and completeness of questionnaire collection rates	Questionnaires Interviews/ Focus groups Anthropometrics WHR, WHtR BP, PR Assess recruitment numbers and consent, procedure adherence, and completeness of questionnaire collection rates DEXA scan	Questionnaires Interviews/ Focus groups Anthropometrics BP, PR, WHR, WHtR Assess recruitment numbers and consent, procedure adherence, and completeness of questionnaire collection rates	Questionnaires Interviews/ Focus groups Anthropometrics BP, PR WHR, WHtR Assess recruitment numbers and consent, procedure adherence, and completeness of questionnaire collection rates	Questionnaires Interviews/ Focus groups Anthropometrics PR, BP WHT, WHtR Assess recruitment numbers and consent, procedure adherence, and completeness of questionnaire collection rates 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



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• Translational Research in Pediatrics Group

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