Electronic Supplementary Material

Performance evaluation of a semi-automated method for [^{18}F]FDG uptake in abdominal visceral adipose tissue

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LITERATURE SEARCH details

Search strategy and selection criteria

Studies were identified by a search of the PubMed and Embase database using the following keyword: synonyms for [^{18}F]-2—fluoro-2-deox-D-glucose (FDG) AND synonyms for abdominal fat AND published between 1 January 1995 up to 1 November 2016 (details search strategy are presented in Suppl. Table 1).

To be selected for this review, studies had to fulfill the following eligibility criteria: (1) [^{18}F]FDG used as a tracer in PET; (2) [^{18}F]FDG uptake reported as standardized uptake value (SUV, i.e. the decay-corrected tissue radioactivity concentration divided by the administered dose per body weight); (3) [^{18}F]FDG uptake reported of adipose abdominal tissue; (4) published in the English language.

Prospective and retrospective studies were included. Reviews, abstracts, editorials, and case reports were excluded from this review. The search revealed 248 papers of which 93 were duplicates, so 155 potentially papers were reviewed (details Suppl. Fig. 1). Reviewing titles and abstract revealed 32 potentially eligible for inclusion. After reviewing the full article, 18 papers were excluded because[^{18}F]FDG uptake was not reported as SUV or only reported of the thoracic visceral adipose tissue or only the visceral fat area or volume was reported and not the [^{18}F]FDG uptake. Eventually, 14 studies met all inclusion (details presented in Suppl. Table 2).

Results

SUV parameter and reported values

There are four different parameters to report the [^{18}F]FDG uptake as a SUV. Maximal SUV (SUV_{max}) reflects the most intense voxel activity within a region of interest (ROI) or volume of interest (VOI). Mean SUV (SUV_{mean}) reflects the mean SUV within the ROI or VOI. The target to background ratio (TBR) is calculated as the ratio of SUV_{max} of the ROI/VOI and venous blood pool SUV_{mean}, to correct for blood-pool uptake and is described as TBR_{max} or the ratio of the SUV_{mean} value and venous blood pool as TBR_{mean}.

In eight studies, [^{18}F]FDG uptake was reported as SUV_{mean}, in two studies as SUV_{max}, in three studies as TBR_{max}, and one study as TBR_{mean}. In addition, only one study which reported a TBR also reported the blood-pool activity so it was possible to also calculate the background uncorrected SUV value.

Method of measurement

All the included studies used a (LD)CT-scan for anatomic information. Only one study also included healthy individuals who underwent a MR scanning combined with PET. The level of measurement of VAT and SAT differed between the vertebra level Th11-12 and L5/S1. Overall, twelve of the fourteen studies used a manually method by drawing ROIs or selecting VOI on the relevant tissue to measure [^{18}F]FDG uptake. Although, most of the studies used an automatic method first to segment adipose tissue on CT using a Hounsfield Unit (HU) threshold. The amount of ROIs differed between 3 and 25 but the exact amount of ROIs were not always described in detail. There were only two studies who used an automatic 3D isocontour volume of interest to report [^{18}F]FDG uptake.

MATERIALS AND METHODS

Segmentation and quantitative assessment of VAT and SAT

The body area was extracted with thresholding. Noise and air were removed from the image by applying a threshold of CT pixel values ≤274 HU. Bone, muscle or adipose tissue were defined as pixel values ≥ -274 HU. The CT table was automatically removed by calculation of the filled area of each object (connecting components) in a thresholded (pixel values > 184HU) binary images. The object with the largest filled area was always the body.

The body area was dived into bone, muscle an adipose tissue compartments. Bone segmentation was performed by thresholding the body region for all pixels ≥126 HU, muscle segmentation by thresholding all pixel values of -24 to 126 HU, and adipose tissue by thresholding all pixel values of -174 to -24 HU. These cut-off values were based on previous research (manuscript reference 32-36) and histograms of the LDCT slices. All thresholding was followed by morphological removal of noisy pixels. The sum of the bone and muscle masks formed a adipose tissue mask. The abdominal muscular wall was used as a boundary for the separation of the segmented adipose tissue in VAT and SAT areas. Since on the LDCT the abominal muscular wall was not always closed, for example at the linea alba, a line to divide VAT and SAT was drawn manually as an extra reference in all slices.

VAT and SAT areas were calculated in every slices by counting the amount of pixels of each segment. By multiplying this area by the spatial resolution of the CT scan the areas in squared centimeter were provided.

Supplementary Tables

Supplemental Table 1 Search strategy and results

Database	Search string	Results
PubMED	("Fluorodeoxyglucose F18"[Mesh] OR FDG[all fields] OR fluorodeoxyglucose[all fields] OR 18FDG [all fields])	113
	AND	
	("abdominal fat"[Mesh] OR (visceral[all fields] AND fat[all fields]) OR (abdom*[all fields] AND fat[all fields]) OR (abdom*[all fields] AND adipose[all fields]) OR (visceral[all fields] AND adipose[all fields]) OR abdominal tissue[all fields] OR visceral tissue[all fields] OR VAT[all fields])	
	AND	
	("1995-01-01"[PDAT]: "2016-11-01"[PDAT])	
Embase	('fluorodeoxyglucose f 18'/exp ***OR*** (FDG OR fluorodeoxyglucose OR 18FDG):ab,ti)	135
	AND	
	('abdominal fat'/exp OR ((visceral OR abdom*) AND fat):ab,ti OR ((abdom* OR visceral) AND adipose):ab,ti OR ‘abdominal tissue’ OR ‘visceral tissue’ OR VAT):ab,ti)	
	NOT	
	'conference abstract'/it	

Supplemental Table 2: Overview from included studies following literature search

Study	Patients category	Age (years)	N (% males)	BMI	Method/level of SUV measurement	[^{18}F]FDG uptake reported as	[^{18}F]FDG uptake VAT	[^{18}F]FDG uptake SAT
2016 Torigian et al (1)	Heavy smokers and nonsmokers	43±6	20 (100%)	26.2±2.9	The 3D SAT and VAT ROIs generated on CT were transferred to PET images, measurement from the thorax until the pelvis.	SUV_{mean}		
	Chronic heavy cigarette smokers		10 (100%)				0.35±0.10	0.25±0.12
	Nonsmokers (never smokers)		10 (100%)				0.26±0.06	0.22±0.09
2016 Van de Wiele et al (2)	Pancreatic carcinoma	66 (39-80)	38 (66%)	24.6±4.5	ROIs on different slices (lumbal level).	SUV_{mean}	0.6 (range 0.0-1.6)	0.4 (range 0.0-1.0)
2016 Veld et al (3)	MGUS and MM patients	63±11	72 (58%)		ROIs on 4th lumbar vertebra	SUV_{mean}		
	MGUS	64±13	40 (58%)	26.8±3.8			0.22±0.17	0.46±0.20
	MM	62±10	32 (59%)	28.5±5.8			0.85±0.40	0.54±0.73
2016 Pahk et al (4)	Colorectral cancer	64±11.6	131(60%)	?	**VAT**: ROIs were placed on 3 consecutives slices above or below the kidney. **SAT:** 3 ROIs**:** buttock area	SUV_{max}		
	with distant metastasis		13 (?)				1.21±0.39	0.45±0.11
	without distant metastasis		118 (?)				0.76±0.27	0.47±0.15
2016 Im et al (5)	Healthy individuals		49 (59%)		Automatic 3D isocontour VOI using threshold for CT and MR, measurement from the diaphgram to the upper margine of the bladder	SUV_{mean}		
	who underwent FDG PET/CT	54.2±14.7	25 (60%)	23.9±2.9			0.89±0.17	0.53±0.13
	who underwent FDG PET/MR	61.8±13.1	24 (58%)	23.7±2.9			0.50±0.06	0.29±0.06
2015 Bucerius et al (6)	Obese subjects pre and after surgery				**VAT**: ROIs were placed on 3 consecutives slices above or below the kidney. **SAT:** ROIs, presternal	TBR_{max}		
	Pre bariatric surgery	40±9	10 (20%)	41.7±4.3			0.65±0.19 SUV_{max}*: 0.72	0.54±0.30 SUV_{max}*: 0.59
	After bariatric surgery	41±9	10 (20%)	29.7±4.2			0.36±0.11 SUV_{max}**: 0.46	0.44±0.21 SUV_{max}**: 0.56

* = SUVmax calculated as TBRmax*SUV bloodpool (1.10) ** = SUVmax calculated as TBRmax*SUV bloodpool (1.28)

Study	Patients category	Age (years)	N (% males)	BMI	Method/level of SUV measurement	[18F]FDG uptake reported as	[18F]FDG uptake VAT	[18F]FDG uptake SAT
2015 Tahara et al (7)	CV risk screening male and females	62.6±9.3	251 (69%)	23.7±3.1	ROIs on 11 consecutive slices.	TBR_{max}	0.49±0.10	0.27±0.06
	Male	62.7±9.3	172(100%)	24.2±2.8			0.50±0.09	0.28±0.06
	Female	62.4±9.4	79 (0%)	22.7±3.4			0.49±0.12	0.26±0.07
2015 Oliveira et al (8)	Metabolically healthy/abnormal obese & metabolically healthy lean		141 (49%)		ROIs **VAT:** largest cross-section of omental **SAT:** posterolateral	SUV_{mean}		
	Metabolically healthy obese	50.1±14.3	20 (30%)	30.7±5.2			0.46±0.11	0.24±0.06
	Metabolically abnormal obese	57.5±15.5	61 (52%)	32.1±4.5			0.43±0.13	0.24±0.07
	Metabolically healthy lean	49.6±18.9	60 (52%)	23.0±2.6			0.61±0.20	0.26±0.10
2014 Vanfleteren et al (9)	COPD and no COPD subjects	66.6±8.3	42 (71%)	25.1±4.3	ROIs were placed on at least three consecutive slices around the umbilical region.	TBR_{max}		
	No COPD subjects	65.2±8.3	23 (65%)	26.2±4.3			0.28±0.09	0.21±0.09
	COPD subjects	68.4±8.3	19 (79%)	23.7±4.0			0.38±0.18	0.24±0.09
2013 Kodama et al (10)	Impaired glucose tolerance or type 2 diabetes mellitius		53 (75%)		ROIs were placed on the umbilical level and the additional 10 slices.	TBR_{mean}		
	allocated to pioglitazone baseline	68.4±7.3	32 (72%)	25.2±3.5			0.57±0.16	0.30±0.07
	16 weeks of treatment						0.50±0.11	0.29±0.06
	allocated to glimepiride baseline	66.7±9.1	21 (81%)	24.7±3.7			0.54±0.11	0.30±0.06
	16 weeks of treatment						0.58±0.09	0.32±0.06
2013 Reichkednler et al (11)	Moderate overweight Caucasian males (3 treatment groups)	30±6	61 (100%)	28.1±1.8	Manually predefined cubic and spheric volumes (VOI), placed between Th11-12 and L5/S1.	SUV_{mean}	Only reported in a graph. Between 0.2 and 0.4.	
2013 Vosselman et al(12)	Lean adult man after high calorie meal and after cold exposure	23.6±2.1	11 (100%)	22.4±2.1	Selecting cubes as VOI on the relevant tissue. **VAT:** behind the xiphoid **SAT:** L3 - L4	SUV_{mean}		
	After high calorie meal	23.6±2.1	11 (100%)	22.4±2.1			0.49±0.24	0.35±0.15
	After cold exposure		6 (100%)				0.51±0.23	0.18±0.05

Study	Patients category	Age (years)	N (% males)	BMI	Method/level of SUV measurement	[^{18}F]FDG uptake reported as	[^{18}F]FDG uptake VAT	[^{18}F]FDG uptake SAT
2012 Elkhaward et al (13)	Patient with atherosclerosis on stable statin therapy (total)	63.8±6.0	99 (86%)	28.9±3.5	ROI on 5 consecutive slices, close to L2.	SUV_{max}		
	high dose losmapimod baseline	62.3±5.9	34 (85%)	29.8±3.7			0.59±0.11	0.32±0.09
	high dose losmapimod day 84						0.53±0.12	0.30±0.10
	losmapimod lower dose baseline	65.3±5.9	33 (85%)	28.0±3.4			0.58±0.13	0.34±0.09
	losmapimod lower dose day 84						0.56±0.14	0.31±0.08
	placebo baseline	63.7±6.4	32 (88%)	28.9±3.4			0.57±0.13	0.34±0.11
	placebo day 84						0.57±0.08	0.32±0.11
2010 Christen et al (14)	Obese and lean patients staging of primary lung cancer (total)		57 (49%)		ROIs on 25 consecutive slices to create a VOI.	SUV_{mean}		
	Lean patients (BMI < 25 kg/m2)	66.0±14.8	26 (46%)	21.7±0.6			0.88±0.18	0.30±0.09
	Obese patients (BMI > 30 kg/m2)	61.4±10.4	31 (52%)	36.4±3.5			0.81±0.22	0.33±0.08

Values are n (%), mean±SD, median and interquartile range.

BMI = Body Mass Index; CT = Computed Tomography; CV = Cardiovascular; COPD = Chronic Obstructive Pulmonary Disease; FDG = ^{18}F-Fluorodeoxyglucose; HU = Hounsfield Unit; MGUS = Monoclonal Gammopathy of Undetermined Significance; MM = Multiple Myeloma; MR= Magnetic Resonance Imaging; ROIs = Regions Of Interest; SAT = Subcutaneous Adipose Tissue; SUV = Standardized Uptake Value; VAT = Visceral Adipose Tissue; VOI = Volume Of Interest

Supplementary Figures

Supplemental Figure 1 : Flowchart study selection

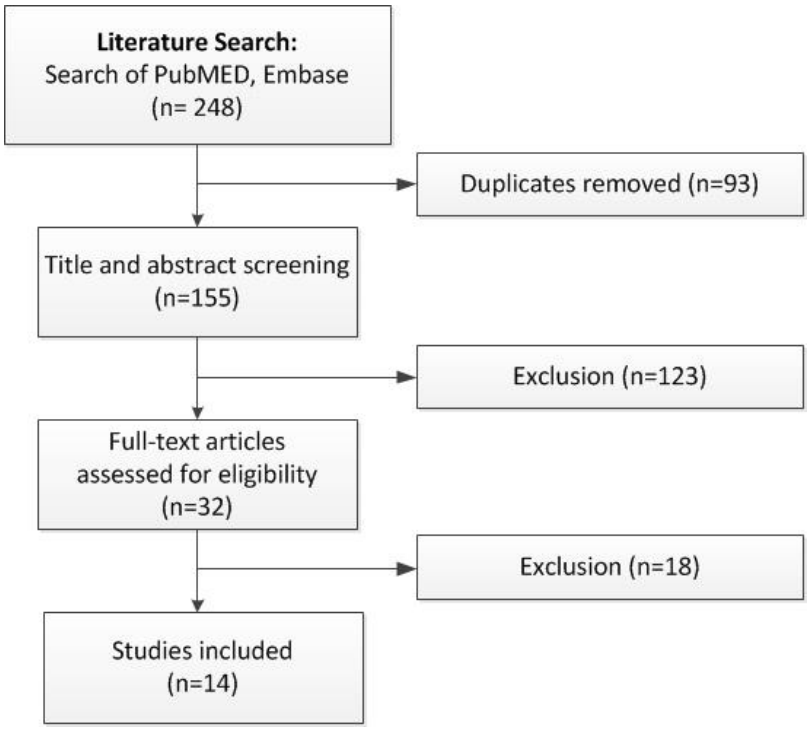

Fig. S1. Flowchart study selection. Reviewing titles and abstract revealed 32 potentially eligible for inclusion. After reviewing the full article, 18 papers were excluded because[^{18}F]FDG uptake was not reported as SUV or only reported of the thoracic visceral adipose tissue or only the visceral fat area or volume was reported and not the [^{18}F]FDG uptake. Eventually, 14 studies met all inclusion.

Supplemental Figure 2: 3D plots of intraclass correlation coefficients for different thresholds and erosions

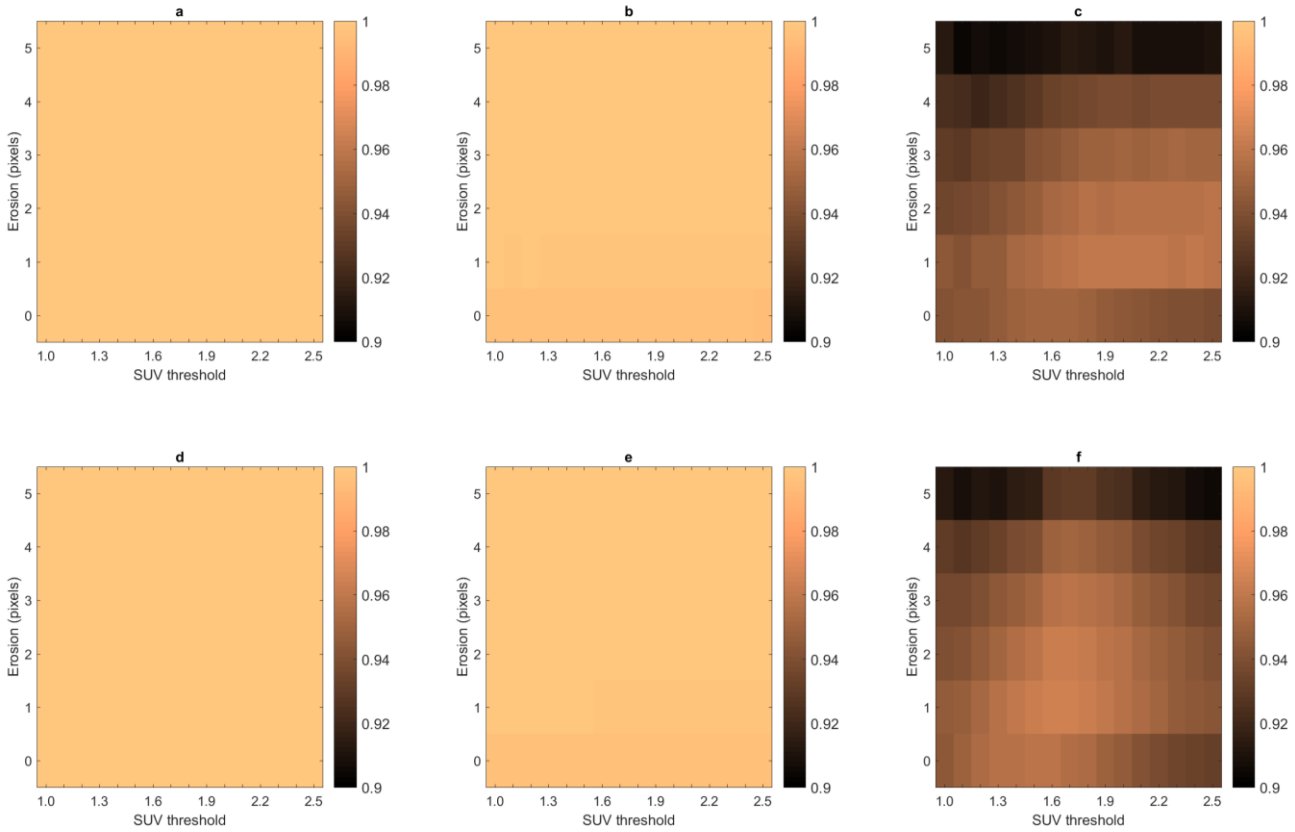

Fig. S2. Each 3D plot represents 96 ICCs calculated for the different SUV thresholds (x-as) and erosions (y-as). The ICCs for interobserver reproducibility for **a** $^{A}SUV_{median}$ VAT and for **d** $^{A}SUV_{mean}$ VAT. The ICCs for intraobserver reproducibility for **b** $^{A}SUV_{median}$ VAT and for **e** $^{A}SUV_{mean}$ VAT. The repeatability ICCs for **c** $^{A}SUV_{median}$ VAT and for **f** $^{A}SUV_{mean}$ VAT.

Supplemental Figure 3: Distribution of SUV values in VAT and SAT

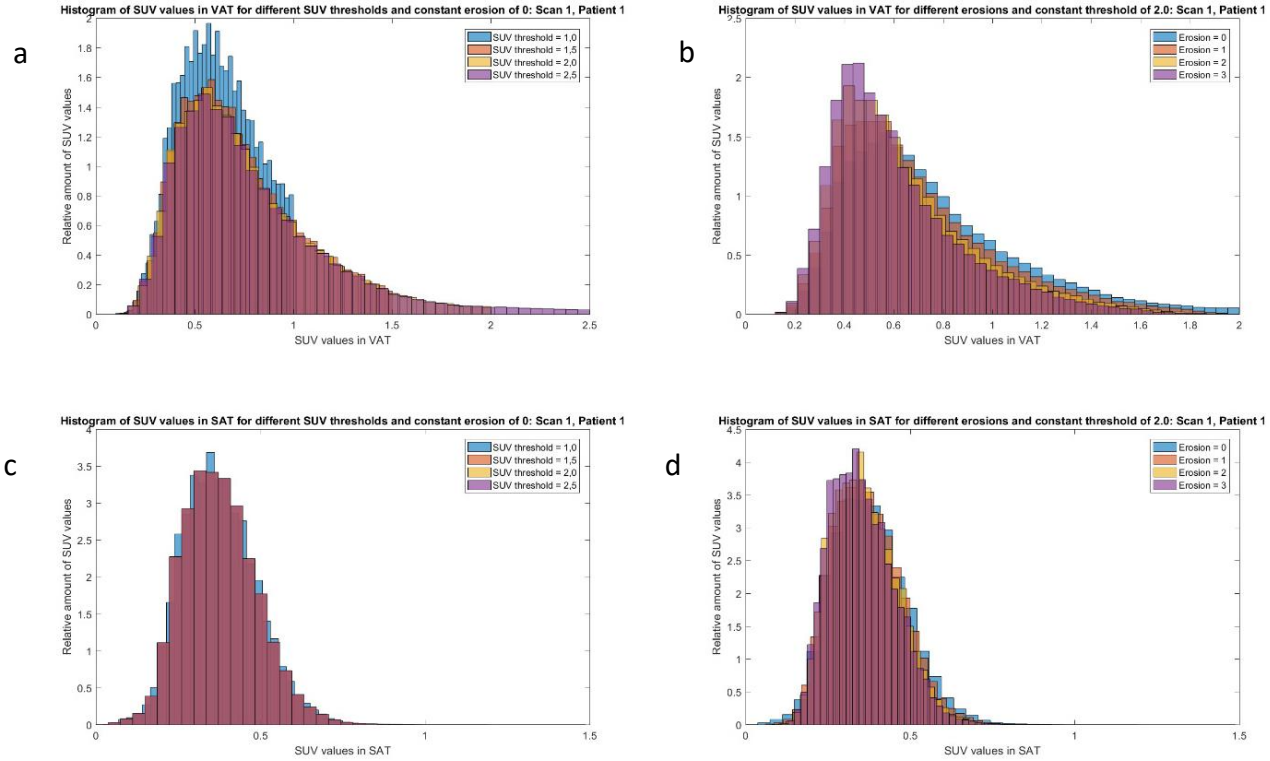

Fig. S3. a Histogram with SUV values in VAT with different SUV thresholds and no erosion and **b** for different erosions and a SUV threshold of 2.0. **c** Histogram with SUV values in SAT with different SUV thresholds and no erosion and **d** for different erosions and a SUV threshold of 2.0.

Supplemental Figure 4: Influence of different SUV threshold on abdominal adipose tissue

Fig. S4. The influence of different SUV threshold on the remaining VAT and SAT (without an erosion).

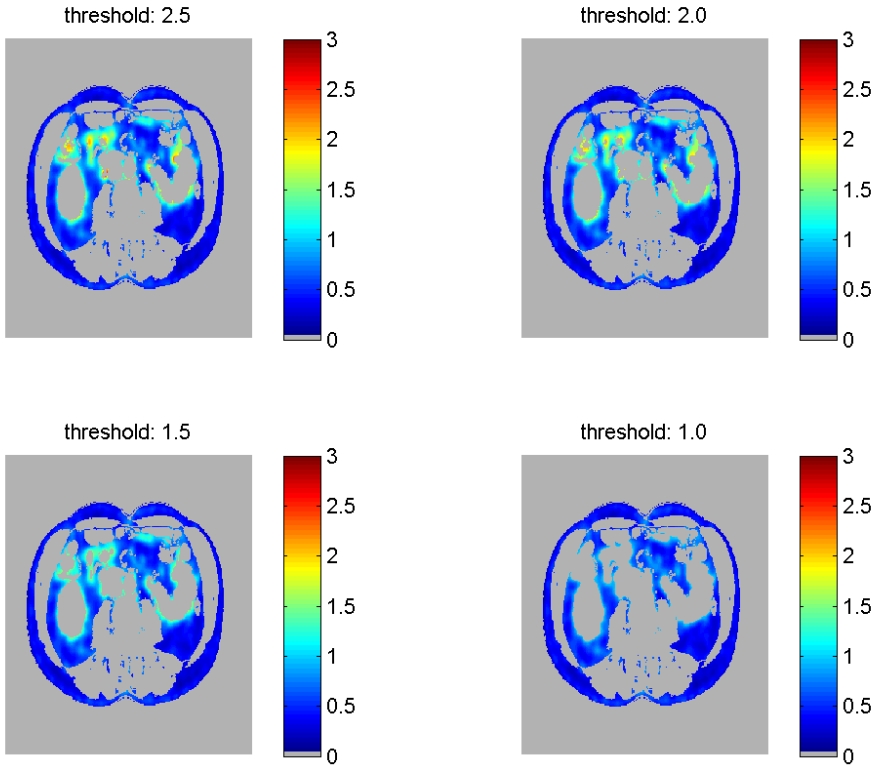

Fig. S4. When the threshold is set at 2.5, there is still some spillover detected in the VAT region. For lower thresholds this spillover, together with SUV values from VAT are removed.

Supplemental Figure 5: Influence of different erosions on abdominal adipose tissue

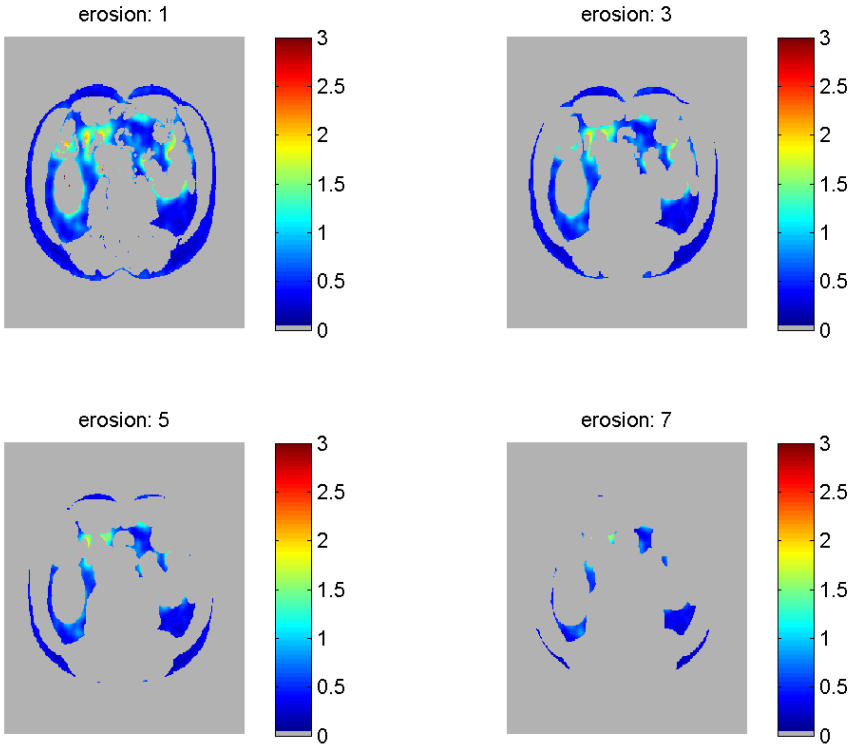

Fig. S5. The influence of different erosions (without a SUV threshold) on the remaining VAT and SAT regions. Most spillover effects are removed for an erosion of 1 pixel. When larger erosions are used also SUV values from VAT and SAT regions are removed.

Supplementary References

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