The Prevalence and Predictors of Active Brown Adipose Tissue in Chinese Adults

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Abstract

Objective—Previous studies have shown active brown adipose tissue (BAT) is present in adults and may play important roles in regulating energy homeostasis. However, nearly every study was done with patients undergoing scanning for cancer surveillance whose metabolism and BAT activity may not reflect that seen in healthy individuals. The objective of this study was to investigate the prevalence and predictors of active BAT in Chinese adults, particularly in healthy individuals.

Design—In this study, a total of 31,088 consecutive subjects with age 18 years old performed PET/CT scans in the site.

Methods—We measured BAT activity via ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography in these subjects who underwent scanning for either routine medical check-up (MC) or cancer surveillance (CS) in Shanghai. Then we investigated the predictors of active BAT, particularly in healthy individuals.

Results—In both groups, the prevalence of BAT was higher in women than men. Using a multivariate logistic analysis, we found in the MC group, age, sex, BMI, and thyroid tissue metabolism were significant predictors of BAT activity. Similarly, in the CS group, age, sex, and BMI were significant predictors of BAT activity, but not thyroid metabolism.

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Conclusions—In Chinese adults, BAT activity correlates inversely with BMI and thyroid metabolic activity, which reinforces the central role of brown fat in adult metabolism and a potential means for treating metabolic syndrome.

Key terms

Positron-emission Tomography and Computed Tomography (PET-CT); Brown Adipose Tissue (BAT); adults; predictor; activity

Introduction

Mammals have two types of adipose tissue, white adipose tissue (WAT) and brown adipose tissue (BAT), which are distinct in both structure and physiologic function [1, 2]. WAT is unilocular and contains a large single vacuole while BAT is multilocular and contains a large number of mitochondria [3]. WAT stores energy and releases adipocytokines, which have been implicated in the impairment of insulin signaling [4]. BAT plays a central role in non-shivering and diet-induced thermogenesis in small mammals [5], and is considered to be a target in the treatment of obesity [6]. It was believed that in humans, BAT only existed in newborns and young children but disappeared or had negligible roles in adults [1, 7]. However, recent studies have demonstrated active BAT is present in adult humans and its presence may be metabolically important [8, 9].

The evidence of the presence of BAT in adult humans has come from ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron-emission tomography/computed tomographic (PET/CT) scans and biopsy. PET/CT showed high uptake of ^{18}F-FDG in supraclavicular and paracervical regions, which were confirmed to be BAT by detection of mRNA and protein expression of uncoupling protein-1 (UCP-1), the BAT-specific thermogenic protein [8, 9]. The physiological significance of the presence of BAT in adult human is not fully understood, but previous studies provided evidence for a potential role of BAT in the regulation of body weight and energy homeostasis [8–11]. Thus, the presence of BAT may help to explain the interindividual differences in metabolism in regard to weight gain in humans [12].

Despite the recent significant progress in understanding adult human BAT, little is known about the prevalence and related factors of active BAT in Chinese adult. Almost all human population studies were done in subjects for cancer surveillance and thus may not reflect BAT behavior in a healthy population. In the present study, we reviewed 31,088 subjects who underwent PET/CT scans at Huashan Hospital in Shanghai and further examined the characteristics of active BAT in this large cohort of adults. Due to the large amount in our cohort, we were able to look at the difference between subjects for medical check-up (MC) and subjects for cancer surveillance (CS), and to clarify the impact of clinical and lifestyle parameters.

Research Design and Methods

Patients

This study followed institutional guidelines and was approved by the ethnic committees of Huashan Hospital, in Shanghai and Beth Israel Deaconess Medical Center and Partners HealthCare, in Boston. Since only medical records were examined, the consent of subjects was not required. From July 2006 to June 2010, a total of 31,088 consecutive subjects with age 18 years old performed PET/CT scans at the Huashan PET/CT centre (geographic coordinates: 31° 12′ N, 121° 30′ E). These scans were done for either medical check-up or cancer surveillance. All scans were obtained using a Siemens Biograph 64 PET/CT scanner.

Data collection

Age, imaging date, sex, and outdoor temperature were collected for all 31,088 subjects. Outdoor temperatures in Shanghai for the scan dates were obtained from the Chinese Meteorological Administration. To evaluate the effects of multiple metabolic parameters on BAT activity, we collected height, body weight, fasting plasma glucose (FPG), medical history, diagnosis, liver triglyceride content, and thyroid metabolic activity for all subjects with detectable BAT and their negative controls, consisting of two subjects who underwent PET/CT scans at the same day but without detectable BAT.

PET/CT scanning and image reconstruction

Before the PET/CT scan, subjects were asked to fast for 8 hours, but had free access to water. After the intravenous injection of 5.55-7.40MBq/kg of 18F-FDG, subjects rested comfortably, with the head, neck, and shoulders supported from the outset of the experiment until imaging began. Room temperature was 21–23°C. Imaging was performed in three-dimensional mode, with emission scans of 1.5 minutes per bed position. The CT scan was used for attenuation correction and localization of the 18F-FDG uptake sites. Both image sets were reconstructed in transaxial, coronal, and sagittal images with a slice thickness of 2 mm. More than three nuclear-medicine physicians interpreted the PET/CT images using OpenPACS and PET/CT Viewer shareware [8]. Each physician reviewed all cases separately, and then they discussed and reached the final consensus.

To examine liver triglyceride content, images from CT scans at thoracic vertebra 11 to 12 were reviewed (Fig. 1B in the Supplementary Appendix). CT attenuation (Hounsfield Unit, HU) was determined in 4 regions of interests (ROIs) for both liver and spleen, each ROI of 120mm^2. ROIs for liver were selected manually to avoid major vessels. The average HU was used to calculate the liver-to-spleen ratio (L/S ratio). Fatty liver was defined as HU< 50 or L/S <1 (Fig. 1C in the Supplementary Appendix) [13, 14].

Thyroid metabolic activity was evaluated by local maximum standard uptake value (SUVmax) of PET scans. The SUVmax of thyroid > 2.5 was considered as thyroid hypermetabolism [15, 16].

Statistical analysis

The data were analyzed with SAS software, version 9.1. Normally distributed continuous variables were compared between study groups with Student's t-test, and non-normally distributed continuous variables were compared with Mann–Whitney U test. The roles of sex, age, BMI, cancer diagnosis, fatty liver and thyroid hypermetabolism as predictors of substantial brown adipose tissue were tested by logistic regression with both univariate and multivariate models.

The subjects were divided into groups corresponding to the upper, middle, and lower thirds of the values for age, BMI, and plasma glucose level; the significance of linear trends across the thirds was tested by assigning each participant the median value for the third and modeling this value as a continuous variable. Missing values for plasma glucose were assigned to the middle third. Odds ratios and 95% confidence intervals were estimated as measures of the magnitude of the associations. All P values presented are two tailed, and values less than 0.05 are considered to be statistically significant.

Results

Prevalence, Age, Body Weight, and Sexual Dimorphism of Brown Adipose Tissue

In the analysis of ^{18}F-FDG PET/CT scans, active brown adipose tissue was considered present if there were areas of tissues that were more than 4 mm in diameter, had the CT density of adipose tissue (–250 to –50 Hounsfield units), and had a maximal SUV of ^{18}F-FDG of at least 2.0 g per milliliter (Fig. 1A in the Supplementary Appendix). This cutoff represented the lower boundary of activity in subjects with detectable brown adipose tissue according to previous study [17], and it was more than 2 SD above the maximal SUV seen in typical depots of white adipose tissue [8]. According to these criteria, 410 of the 31,088 subjects (1.32%) had tissue that was identified by PET/CT as being active brown adipose tissue, which was from 1.3% to 6.7% shown in previous retrospective studies [8, 18–20]. The prevalence of detectable BAT in the medical check-up group was 1.58% [264 of 16,699] while it was 1.01% [146 of 14,389] in the cancer surveillance group ((Fig 1A). In both the medical check-up group and, cancer surveillance group, women had a higher prevalence of active BAT than men (3.16% vs 0.77%, p<0.001; 1.59% vs 0.61%, p<0.001, Fig 1B). The association between the prevalence of active BAT and mean monthly temperature was evaluated by logistic regression. In both medical check-up group (r = –0.759, P<0.0001) and, cancer surveillance group (r = –0.227, P=0.196), the probability of detecting BAT decreased with increasing outdoor temperature (Fig 2 in the Supplementary Appendix). In both groups, the average age of BAT negative subjects was older than BAT-positive subjects (47.78±9.45 years vs. 40.00±8.17 years, P<0.0001; 55.2±14.12 years vs. 43.7±13.38 years, P<0.0001, respectively, Table 1 in the Supplementary Appendix). In addition, in both groups, the body weight was higher in BAT-negative subjects than in BAT-positive subjects (68.78±12.51kg vs. 58.47±10.13kg, P<0.001; 63.10±11.56kg vs. 58.20±9.10kg, P<0.001, Table 1 in the Supplementary Appendix).

Anthropometric and Metabolic Predictors of Active Brown Adipose Tissue

Additional predictors of a high mass of detectable brown adipose tissue were estimated by examining the association of brown adipose tissue with sex, age, BMI, and fasting plasma glucose in the 410 subjects who had detectable brown adipose tissue and a sample of 818 date-matched control subjects who did not show active brown adipose tissue (Table 1). All of these parameters were significantly different between the BAT-positive and BAT-negative subjects in both medical check-up and cancer surveillance groups (Table 2 and 3). In univariate analyses of medical check-up subjects (Table 4), BAT was more likely to be detected in women (P<0.0001), patients in the bottom third for age (younger than 39.2 years) (P<0.0001), the least obese patients (P<0.0001), and those who had no fatty liver (P<0.0001) (Table 4). The univariate analyses of cancer surveillance patients showed results with similar significance (Table 5).

In age- and sex- adjusted multivariate analyses, BMI in the cancer surveillance patients remained significant (Table 5), while in the medical check-up subjects, BMI and thyroid hypermetabolism remained statistically significant (Table 4). The likelihood of having detectable brown adipose tissue was greater in the least obese subjects by a factor of approximately 4; and in those medical check-up subjects who had no thyroid hypermetabolism by a factor of approximately 2 (Table 4 and 5). Thus, brown adipose tissue was found most frequently in young women who had lower BMI.

Medical check-up versus cancer surveillance subjects

264/410 (64.39%) of subjects in the BAT positive cohort did not have a diagnosis of cancer and underwent PET/CT for medical check-up. There were three different factors between the cancer surveillance patients and the medical check-up subjects. The check-up subjects in the BAT positive cohort were younger (40.00 vs. 43.70, P=0.0027) and with lower fasting plasma glucose levels (4.88 vs. 4.99, P=0.0330) (Table 1).

Discussion

Obesity is a significant cause of morbidity and mortality, and there has been considerable recent interest in studying the physiology of BAT in humans, given its protective role against obesity in animal studies [21, 22]. Recently, several studies led to a paradigm shift in our comprehension of the potential role of BAT in adult humans. A greater understanding of BAT function could thus help to develop treatment strategies for obesity, especially as many have shown both retrospectively [8, 18] and prospectively [23] that there is an inverse correlation between BAT activity and obesity. However, the retrospective studies were done using patients with a history of cancers and in cohorts that were of mostly European decent, and the prospective studies to date have been too small and only in healthy volunteers, so our understanding of BAT activity remains unknown in large, healthy populations, and in the Chinese in particular.

PET-CT has long been used to stage cancers. Recently, it has been used to detect malignant cancers in asymptomatic individuals [24]. Our study took advantage of this and included 16,699 healthy subjects in this cohort. To our knowledge, our report is the largest study of

its kind documenting the prevalence and predictors of active BAT in healthy adults. We found substantial collections of brown adipose tissue in 1.32% of subjects which was lower than previous studies [8, 25]. Factors such as race, region, underlying disease, type and size of study, and ambient temperature, likely contributed to the different outcomes. The significantly lower prevalence of detectable BAT in the cancer surveillance group than medical check-up group (1.01% vs. 1.58%, P<0.001) may result from the latter being a younger cohort, though other metabolic parameters should also be considered. Our results also suggested that despite some quantitative differences between the CS and MC groups, most of findings were qualitatively similar, including age, sex, and BMI. This indicated that studies done in CS patients are likely reflective of the general population.

In unstimulated conditions, the reported prevalence of active BAT in previous studies were from 4.6% to 6.8% [8, 25, 26], which were higher than that (1.32%, 410 of 31,088 subjects) reported here. As it has been shown that ambient temperature and photoperiod is correlated with the prevalence of active BAT, the various prevalence can at least partially be attributed to the different locations. The latitude of geographic coordinates for the three locations where the previous studies were done is 42°21′ North (Boston, USA), 45°24′ North (Sherbrooke, Canada) and 52°58′ North (Nottingham, UK), while our location is 31°12′ North (Shanghai, China). The mean annual temperature for these four cities is 11° in Boston, 5° in Sherbrooke, 9° in Nottingham and 16° in Shanghai (Table 2 in the Supplementary Appendix). Obviously, Shanghai has the warmest climate among these four locations. Consistent with previous findings [25, 26], here we also showed an inverse correlation between the prevalence of detectable BAT and mean monthly temperature. In addition to the location and temperature, the ethnics may also contribute to the various prevalence, which need to be clarified in future studies.

Our study also demonstrated significantly increased prevalence of BAT in female subjects, which is consistent with other studies [8, 18]. Possible sources for this sex-based difference may be seen in rodents, where female rats have higher levels of UCP1 in the interscapular BAT depot compared to males when housed at the same temperature, suggesting that they may have a lower threshold temperature for cold-induced thermogenesis [27]. BAT also expresses oestrogen receptors which may further explain these differences [1], since the decrease in sex hormone levels with increased age could be a cause of BAT atrophy. As a result, these subjects will be in a metabolic state with an increased propensity to develop obesity [28]. Interestingly, the BMI was lower in the BAT positive group than in negative group in both MC and CS groups, which could be highly relevant in terms of human energy expenditure. Thus, BAT was found most frequently in young healthy women with lower BMI in cold days.

In BAT positive subjects, age was lower in the medical check-up group than in the cancer surveillance group. Cancer usually occurs in older people, thus it is easy to understand the lower age in check-up group. And the findings in the medical check-up group were more representative of the general population than the cancer surveillance group.

In the medical check-up groups, there appeared to be an inverse correlation between the probability of detecting BAT and thyroid hypermetabolism in a multivariate analysis (P =

0.0114). Thyroid hormones are known to be the main regulators of heat generation during shivering and non-shivering cold adaptation [29]. When exposed to cold or a lesser degree after meals, the expression of UCP1 is induced by the synergistic action of norepinephrine (NE) and thyroid hormones in animals [1]. But it is unclear what the effect of the thyroid hormones has on BAT activity in adult humans. Recently, Skarulis et al. have shown that levothyroxine replacement increased ^{18}F-FDG uptake of BAT in a hypothyroid patient. Consistent with the PET/CT data, both the suprascapular and periumbilical adipose tissue samples of the patient showed significant type 2 deiodinase (D2) activity that was not present in a control sample obtained from another subject [30]. In our study, the PET/CT assessment of thyroid metabolism has high sensitivity, but poor specificity. It cannot reflect the thyroid hormones levels directly. Moreover, BAT expresses D2, which converts T4 into active T3, so thyroid gland metabolism and serum thyroid hormones may not reflect the microenvironment of the brown adipocytes. Further studies are required to understand the effect of thyroid hormones on human BAT activation.

In summary, our very large retrospective study demonstrates that the parameters affecting the detection of BAT activity are similar in both healthy subjects undergoing PET/CT for a medical check-up and those patients being scanned for cancer surveillance. Detectable BAT activity correlates positively with more fixed parameters such as climate, age, and sex, but also with factors that can be modified, including BMI, liver fat content, and liver triglyceride content. Given the metabolic benefits seen in animal models with the activation of BAT, our study reinforces the goal of increasing BAT mass and activity through both lifestyle and pharmacologic interventions as a way to treat obesity and its associated metabolic complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

BAT	brown adipose tissue
PET/CT	positron emission tomography/computed tomography
MC	medical check-up
CS	cancer surveillance

WAT	white adipose tissue
^{18}F-FDG	^{18}F-fluorodeoxyglucose
UCP-1	uncoupling protein-1
FPG	fasting plasma glucose
HU	Hounsfield Unit
ROI	region of interest
L/S ratio	liver–spleen Hounsfield ratio
SUVmax	maximum standard uptake value
NE	norepinephrine
D2	type 2 deiodinase

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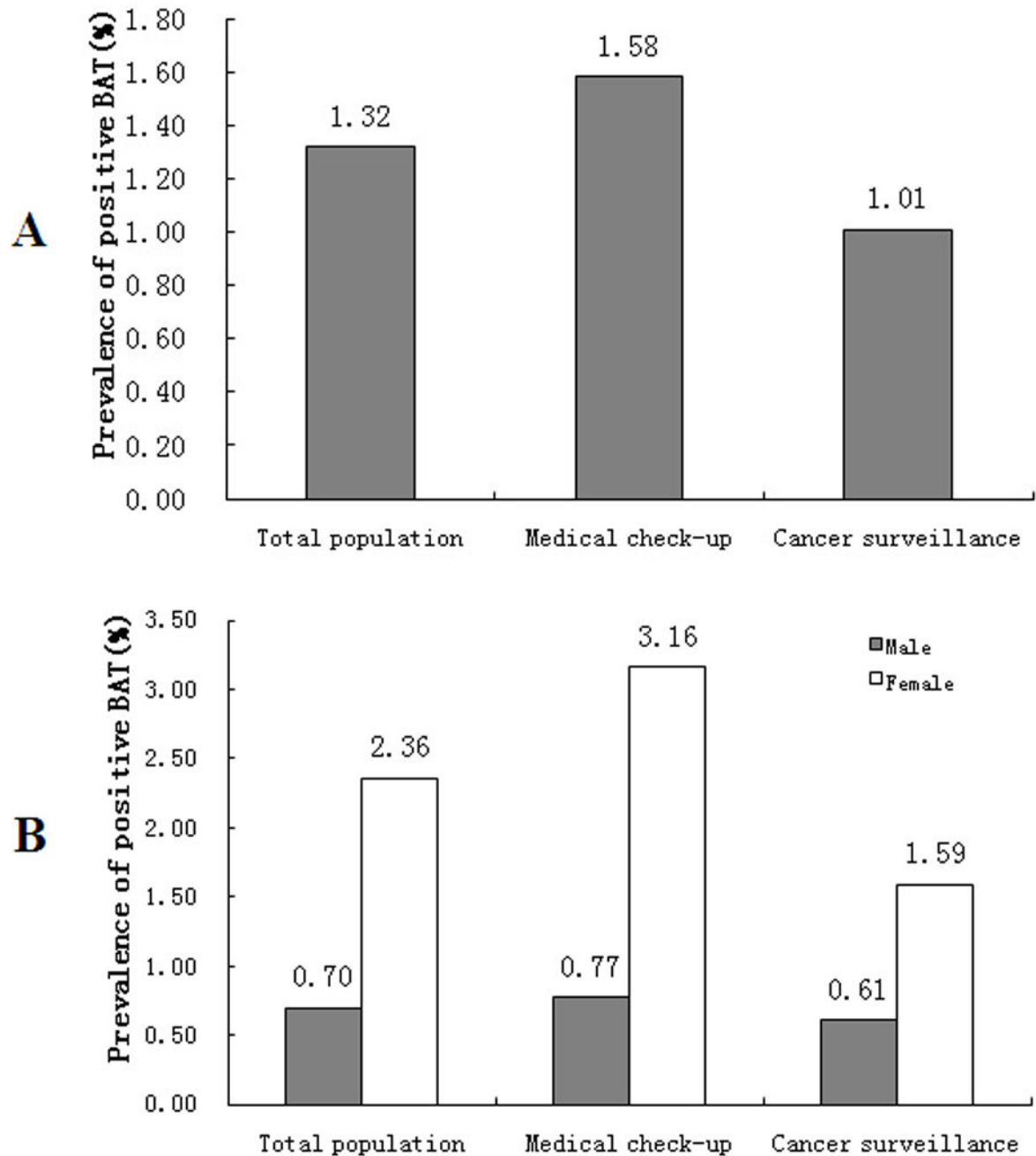
Figure 1. The prevalence of active BAT in both cancer surveillance patients and medical check-up subjects

In figure 1A, it shows that in all adult subjects, the prevalence of active BAT is 1.32% while in those patients for cancer surveillance, it is 1.01% and in those for medical check-up, it is 1.58% (P<0.001, medical check-up vs. cancer surveillance). Figure 1B shows the prevalence of active BAT in men and women. In both cancer surveillance patients and medical check-up subjects, the prevalence of detective BAT is higher in women than in men (1.59% vs. 0.61%, 3.16% vs. 0.77%, P<0.0001, respectively).

Table 1

Clinical characteristics of BAT positive subjects in medical check-up and cancer surveillance patients.

Characteristics	Medical check-up (N=264)	Cancer surveillance (N=146)	P Value
Female - no. (%)	179 (67.80%)	94 (64.38%)	0.5125
Age – years	40.00±8.17	43.70±13.38	0.0027
Age – tertiles			0.0002
<39.7 y - no. (%)	130 (49.24%)	59 (40.41%)	
39.7–50.7 y - no. (%)	85 (32.20%)	33 (22.60%)	
>50.7 y - no. (%)	49 (18.56%)	54 (36.99%)	
BMI - kg/m^2	21.10±2.46	21.00±2.43	0.6924
BMI – tertiles			0.4193
<21.5 kg/m^2 - no. (%)	164 (62.12%)	88 (60.27%)	
21.5–24.7 kg/m^2 - no. (%)	82 (31.06%)	52 (35.62%)	
>24.7 kg/m^2 - no. (%)	18 (6.82%)	6 (4.11%)	
Glucose - mmol/l	4.88±0.52	4.99±0.50	0.0330
Glucose - tertiles			0.2520
<4.8 mmol/l - no. (%)	110 (41.98%)	47 (33.57%)	
4.8–5.3 mmol/l - no. (%)	77 (29.39%)	46 (32.86%)	
>5.3 mmol/l - no. (%)	75 (28.63%)	47 (33.57%)	
Fatty Liver			0.7624
NO - no. (%)	227 (85.98%)	128 (87.67%)	
YES - no. (%)	37 (14.02%)	18 (12.33%)	
Thyroid Hypermetabolism			0.1999
NO - no. (%)	200 (75.76%)	102 (69.86%)	
YES - no. (%)	64 (24.24%)	44 (30.14%)	

Note: In medical check-up group, data on BMI were missing for 4 BAT-negative subjects and 4 BAT-positive subjects.

In cancer surveillance group, data on BMI were missing for 6 BAT-negative subjects and 1 BAT-positive subject. Data on FBG were missing for 6 BAT-negative subjects and 6 BAT-positive subjects.

Table 2

Clinical characteristics of BAT positive subjects and date-matched negative controls in medical check-up subjects.

Characteristics	Medical check-up		
	BAT negative (N=528)	BAT positive (N=264)	P Value
Female - no. (%)	223 (42.40%)	179 (67.80%)	<0.0001
Age – years	44.58±8.06	40.00±8.17	<0.0001
Age – tertiles			<0.0001
<39.2 y - no. (%)	140 (26.52%)	130 (49.24%)	
39.2–45.7 y - no. (%)	218 (41.29%)	85 (32.20%)	
>45.7 y - no. (%)	170 (32.20%)	49 (18.56%)	
BMI - kg/m^2	24.80±3.22	21.10±2.46	<0.0001
BMI – tertiles			<0.0001
<21.7 kg/m^2 - no. (%)	92 (17.42%)	164 (62.12%)	
21.7–25.0 kg/m^2 - no. (%)	182 (34.47%)	82 (31.06%)	
>25.0 kg/m^2 - no. (%)	254 (48.11%)	18 (6.82%)	
Glucose - mmol/l	5.05±0.85	4.88±0.52	0.0006
Glucose – tertiles			0.2789
<4.7 mmol/l - no. (%)	192 (36.50%)	110 (41.98%)	
4.7–5.0 mmol/l - no. (%)	177 (33.65%)	77 (29.39%)	
>5.0 mmol/l - no. (%)	157 (29.85%)	75 (28.63%)	

Table 3

Clinical characteristics of BAT positive patients and date-matched negative controls in cancer surveillance patients.

Characteristics	Cancer surveillance		
	BAT negative (N=292)	BAT positive (N=146)	P Value
Female - no. (%)	136 (46.58%)	94 (64.38%)	0.0004
Age – years	45.67±10.62	43.70±13.38	0.1216
Age – tertiles			0.0085
<39.7 y - no. (%)	80 (27.40%)	59 (40.41%)	
39.7–50.7 y - no. (%)	75 (25.68%)	33 (22.60%)	
>50.7 y - no. (%)	137 (46.92%)	54 (36.99%)	
BMI - kg/m^2	24.27±3.39	21.00±2.43	<0.0001
BMI – tertiles			<0.0001
<21.5 kg/m^2 - no. (%)	64 (21.92%)	88 (60.27%)	
21.5–24.7 kg/m^2 - no. (%)	97 (33.22%)	52 (35.62%)	
>24.7 kg/m^2 - no. (%)	131 (44.86%)	6 (4.11%)	
Glucose - mmol/l	5.23±0.98	4.99±0.50	0.0011
Glucose – tertiles			0.2337
<4.8 mmol/l - no. (%)	94 (32.87%)	47 (33.57%)	
4.8–5.3 mmol/l - no. (%)	68 (23.78%)	46 (32.86%)	
>5.3 mmol/l - no. (%)	124 (43.36%)	47 (33.57%)	

Table 4

Predictors of detectable BAT based on PET–CT scanning in medical check-up subjects.

Variable	Medical check-up			
	Univariate Analysis		Multivariate logistic regression	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Sex				
Female vs. male	2.861 (2.097–3.904)	<0.0001	1.405 (0.853–2.314)	0.1815
Years of age				
39.2–45.7 vs. <39.2	0.420 (0.297–0.594)	<0.0001		
>45.7 vs. <39.2	0.310 (0.209–0.462)	<0.0001	0.745 (0.591–0.939)	0.0126
Body-mass index				
21.7–25.0 vs. <21.7	0.253 (0.175–0.364)	<0.0001		
>25.0 vs. <21.7	0.040 (0.023–0.068)	<0.0001	0.237 (0.185–0.305)	<0.0001
Fasting plasma glucose				
4.7–5.0 vs. <4.7	0.754 (0.529–1.074)	0.1177		
>5.0 vs. <4.7	0.827 (0.577–1.186)	0.3028	1.193 (0.948–1.502)	0.1321
Fatty liver				
Yes vs. no	0.323 (0.218–0.478)	<0.0001	0.695 (0.430–1.123)	0.1368
Thyroid Hypermetabolism				
Yes vs. no	0.853 (0.607–1.199)	0.3612	0.595 (0.398–0.890)	0.0114

Note: Logistic regression is based on the age- and sex- adjusted results.

Table 5

Predictors of detectable BAT based on PET–CT scanning in cancer surveillance patients.

Variable	Cancer Surveillance			
	Univariate Analysis		Multivariate logistic regression	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Sex				
Female vs. male	2.073 (1.377–3.122)	0.0005	1.057 (0.586–1.906)	0.8546
Years of age				
39.7–50.7 vs. <39.7	0.597 (0.351–1.013)	0.0561		
>50.7 vs. <39.7	0.534 (0.337–0.847)	0.0077	0.976 (0.736–1.295)	0.8683
Body-mass index				
21.5–24.7 vs. <21.5	0.390 (0.245–0.621)	<0.0001		
>24.7 vs. <21.5	0.033 (0.014–0.080)	<0.0001	0.221 (0.155–0.316)	<0.0001
Fasting plasma glucose				
4.8–5.3 vs. <4.8	1.276 (0.773–2.106)	0.3396		
>5.3 vs. <4.8	0.715 (0.446–1.148)	0.1647	1.058 (0.788–1.421)	0.7062
Fatty liver				
Yes vs. no	0.360 (0.207–0.628)	0.0003	0.646 (0.335–1.246)	0.1923
Thyroid Hypermetabolism				
Yes vs. no	1.086 (0.703–1.679)	0.7097	0.672 (0.392–1.152)	0.1485

Note: Logistic regression is based on the age- and sex- adjusted results.