# Outdoor Temperature, Age, Sex, Body Mass Index, and Diabetic Status Determine the Prevalence, Mass, and Glucose-Uptake Activity of $^{18}$F-FDG-Detected BAT in Humans

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**Context:** In humans, the prevalence, mass, and glucose-uptake activity of $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG)-detected brown adipose tissue (BAT), which are expectedly enhanced by a cold stimulus, also appear modulated by other factors that still have to be disentangled.

**Objective:** The objective of the study was to investigate the factors determining the prevalence, mass, and glucose-uptake activity of $^{18}$F-FDG-detected BAT in humans.

**Research Design and Methods:** We retrospectively analyzed all $^{18}$F-FDG positron emission tomography/computed tomography examinations performed between January 2007 and December 2008 at our institution for $^{18}$F-FDG uptake within the cervical/supraclavicular, mediastinal, paravertebral, and perirenal fat areas. The influence of outdoor temperature, sex, age, body mass index (BMI), plasma glucose level, diabetes diagnosis, day length, and cancer status on the prevalence, mass, and glucose-uptake activity of $^{18}$F-FDG-detected BAT depots was investigated.

**Results:** Three hundred twenty-eight of the 4842 patients (6.8%) had $^{18}$F-FDG-detected BAT. The prevalence of $^{18}$F-FDG BAT was negatively associated with outdoor temperature ($P < 0.0001$), age ($P < 0.0001$), BMI ($P < 0.0001$), and diabetes status ($P = 0.0003$). Moreover, there was a significant age $\times$ sex interaction for the prevalence of $^{18}$F-FDG BAT (the younger the subjects, the greater the sex difference). The mass and glucose-uptake activity of $^{18}$F-FDG-detected BAT also decreased with increasing outdoor temperature ($P < 0.0001$), age ($P < 0.0001$), and BMI ($P < 0.0001$). They were lower in men than in women ($P < 0.001$) and lower in diabetic than in nondiabetic patients ($P = 0.0002$).

**Conclusions:** The present study identifies outdoor temperature, age, sex, BMI, and diabetes status as determinants of the prevalence, mass, and glucose-uptake activity of $^{18}$F-FDG-detected BAT. **(*J Clin Endocrinol Metab* 96: 192–199, 2011)**

Brown adipose tissue (BAT) is a specialized tissue, the thermogenic potential of which is such that it allows small mammals to live in a cold environment without shivering (1, 2). Its thermogenic power is conferred by uncoupling protein 1 (UCP1), a mitochondrial protein uniquely found in brown fat cells (3). BAT thermogenic activity depends on the adrenergic stimulation of brown adipocytes (4, 5). Evidence has accumulated throughout the years,

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Abbreviations: BAT, Brown adipose tissue; BMI, body mass index; CT, computed tomography; $^{18}$F-FDG, $^{18}$F-fluorodeoxyglucose; LBW, lean body weight; PET, positron emission tomography; SUV, standardized uptake value; UCP1, uncoupling protein 1.

mainly from studies carried out in rodents, to suggest that BAT thermogenesis is involved in energy balance (4, 6).

Up until recently, the conviction was that BAT in humans was detected only in newborn infants. However, in the past few years, positron emission tomography (PET)/computed tomography (CT) scanning investigations revealed the presence of cervical, supraclavicular, mediastinal, paravertebral, and perirenal fat depots readily taking up $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) in adults (7), which were identified and characterized as BAT (8–12). Importantly, BAT needs to be metabolically activated to be detected by PET/CT scanning.

The reported prevalence of BAT taking up $^{18}$F-FDG in adults varies considerably, depending on the studies. In the studies with large cohorts of patients evaluated for cancer, $^{18}$F-FDG BAT prevalence was found to be low (ranging between 5 and 10%) (8, 13), whereas in investigations with young cold-exposed subjects, the prevalence was reported to be very high (close to 100%) (9, 10). Predictably, the ambient temperature at the time of the PET/CT assessments is a critical factor for determining the ability of BAT to take up $^{18}$F-FDG and therefore to become detected (8–10, 12–15). That cold exposure can increase the prevalence of $^{18}$F-FDG BAT is predictable, considering the fact that BAT is a thermogenic organ. Interestingly, however, a cold stimulus does not appear to act alone or perhaps to be the sole factor rendering BAT detected by PET/CT scanning. Factors such as sex (8, 13–18), age (8, 11, 12, 14–18), body mass index (BMI) (9, 11, 12, 18), plasma glucose (19), and day length (13) have all been suggested to be determinants of $^{18}$F-FDG uptake in BAT. Nonetheless, there is still controversy with regard to the relative importance of all those factors in determining the prevalence, mass, and glucose-uptake activity of $^{18}$F-FDG BAT. The purpose of this study was to examine the determinants of the prevalence, mass, and glucose-uptake activity of $^{18}$F-FDG-detected BAT in a large cohort of subjects who underwent PET/CT examination for cancer diagnosis and staging.

## Subjects and Methods

A total of 8095 consecutive $^{18}$F-FDG PET/CT scans were performed from January 2007 to December 2008 at the Centre Hospitalier Universitaire de Sherbrooke (Sherbrooke, Province of Québec, Canada). All PET/CT scans were performed using either a Gemini GXL or a Gemini TF PET/CT scanner (Philips Medical Systems, Best, The Netherlands). The large majority of scans were performed for cancer detection. Scans that did not include all possible BAT areas were excluded. Patients mainly came from cities within 150 km from Sherbrooke. Patients were instructed to fast 4 h before their scan. After the injection of $^{18}$F-FDG, patients sat for 60 min in a room in which the ambient temperature was set at 24 C. Subjects were neither warmed nor instructed to avoid cold before the PET/CT examinations. We thus evaluated retrospectively 6652 $^{18}$F-FDG PET/CT scans from 4842 patients (2370 women, 2472 men; mean age ± SE, 62 ± 0.2 yr; age range 2–94 yr) for $^{18}$F-FDG uptake within the cervical/supraclavicular, mediastinal, paravertebral, and perirenal fat areas. These areas have been previously suggested to be BAT depots in PET/CT studies (7, 9–12), and recent histological examinations have demonstrated that the cervical/supraclavicular fat depots possess the characteristics of BAT (9–12). For patients who underwent serial $^{18}$F-FDG PET/CT examinations during the 2-yr period, only the first scan was used for analyses. Data on sex, age, weight, BMI, plasma glucose level, and diabetes diagnosis were obtained for all patients. For diabetes diagnosis, we can assume that most patients had type 2 diabetes because more than 75% of our patients with diabetes were above 60 yr old, and only one patient was younger than 30 yr old, and 90% of the diabetes population have type 2 diabetes. Lean body weight (LBW) was calculated using the following formulas: men, LBW = [1.10 × weight (kilograms)] − [128 × (weight [kilograms]/height [centimeters])$^2$]; women, LBW = [1.07 × weight (kilograms)] − [148 × (weight [kilograms])/height [centimeters])$^2$]. Outdoor temperature in Sherbrooke for the day of the scan was obtained from Environment Canada (http://climate.weatheroffice.ec.gc.ca/climatedata/canada_f.html). Day length was obtained from the National Research Council Canada (http://www.nrc-cnrc.gc.ca/eng/services/hia/sunrise-sunset.html). PET/CT reports and medical records were reviewed for cancer diagnosis. If the diagnosis was not available, it was classified as undetermined.

Patients were considered to have $^{18}$F-FDG BAT when the following criteria were met: 1) $^{18}$F-FDG uptake was in the cervical/supraclavicular, mediastinal, paravertebral, and/or perirenal areas; 2) $^{18}$F-FDG uptake had a maximum standardized uptake value (SUV) 1.0 g/ml or greater (an indicator of $^{18}$F-FDG uptake intensity); and 3) the tissue corresponded to the density of adipose tissue on CT (−100 to −10 Hounsfield units). For patients exhibiting $^{18}$F-FDG BAT, the mean and maximum SUVs for each identified depot were determined using a commercial fusion software (MIM software; MIMvista Corp., Cleveland, OH). The volume of $^{18}$F-FDG BAT was quantified by autocontouring each identified individual BAT depot (with a SUV ≥ 1.0 g/ml). BAT glucose-uptake activity was calculated by multiplying the BAT volume by the mean SUV. For BAT mass calculations, we assumed that fat has a density of 0.90 g/ml (20).

The project was approved by the Ethics Committee of the Centre Hospitalier Universitaire de Sherbrooke.

### Statistics

All analyses were performed using the R software (http://www.r-project.org/), version 2.4.1. To assess the differences between patients with and without BAT $^{18}$F-FDG uptake, Student's *t* test was used for normally distributed variables, the Wilcoxon-Mann Whitney *U* test was used for nonnormally distributed variables, and the $\chi^2$ test was used for proportions. The determinants of the prevalence of $^{18}$F-FDG-BAT were identified by a logistic regression with the use of univariate and multivariate models. The determinants of PET/CT-detected BAT patterns were identified using a multinomial logistic regression with the use of a multivariate model. The predictors of the mass and glucose-uptake activity of $^{18}$F-FDG-BAT were identified using the multivariate Tobit model (21). The Tobit model is specifically designed for variables distributed with a large percentage of cases at

**TABLE 1.** Clinical and physical characteristics of patients with and without BAT $^{18}$F-FDG uptake[a]

| Characteristics | BAT $^{18}$F-FDG uptake | |
|---|---|---|
| | No | Yes |
| n | 4514 | 328 |
| Age (yr) | 62.7 ± 0.2 | 54.4 ± 0.8[b] |
| Weight (kg) | 73.8 ± 0.3 | 65.5 ± 0.8[b] |
| Height (cm) | 166 ± 0.1 | 163 ± 0.5[b] |
| BMI (kg/m$^2$) | 26.8 ± 0.1 | 24.6 ± 0.2[b] |
| Glucose (mmol/liter) | 5.9 ± 0.02 | 5.6 ± 0.03[b] |
| Outdoor temperature (C)[c] | 6.5 ± 0.2 | 2.9 ± 0.7[b] |
| Diabetes (%) | 11.6 | 1.8[b] |
| Active cancer (%) | 54.8 | 52.4 |

[a] Data are mean ± SE or percent.

[b] $P < 0.05$ *vs.* patients without BAT $^{18}$F-FDG uptake (Student's *t* test for normally distributed variables and Wilcoxon-Mann-Whitney *U* test for nonnormally distributed variables, $\chi^2$ test for proportions).

[c] Temperature on the day of the scan.

the lower or upper limit. This model appeared as being of relevant use in this study because a large percentage of subjects in our cohort did not exhibit $^{18}$F-FDG-BAT. The dependent variables were assumed to be normally distributed and left truncated at zero. All *P* values presented are two sided and those less than 0.05 are considered statistically significant.

## Results

### Determinants of $^{18}$F-FDG-detected BAT prevalence

We observed $^{18}$F-FDG BAT in 328 of the 4842 patients (6.8%). The individuals with BAT $^{18}$F-FDG uptake were on average younger and had lower body weight, BMI, and plasma glucose levels compared with the individuals without BAT $^{18}$F-FDG uptake (Table 1). The mean outdoor temperature on the day of the scan was lower for patients with $^{18}$F-FDG BAT compared with patients without $^{18}$F-FDG BAT. In both the patients with and without $^{18}$F-FDG BAT, approximately half of the patients had cancer (active disease), a proportion that was not different between the two subgroups. In patients with $^{18}$F-FDG BAT, the cervical/supraclavicular location was the most frequent (94.2% of subjects), followed by the paravertebral (61.6% of subjects), mediastinal (28.0% of subjects), and the perirenal (20.1% of subjects) (Table 2 and Supplemental Fig. 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). Most commonly, individuals with BAT $^{18}$F-FDG uptake had only cervical/supraclavicular depots (33.5%), whereas only 11.9% of individuals exhibited $^{18}$F-FDG-BAT in all four depots (Table 2). Approximately 60% of the patients had $^{18}$F-FDG uptake in cervical/supraclavicular BAT only or cervical/supraclavicular and paravertebral BAT.

From univariate analyses, lower outdoor temperature, sex (female), lower age, lower BMI, higher LBW, lower plasma glucose levels, nondiabetic status, and shorter day length were all predictive of a higher prevalence of $^{18}$F-FDG-detected BAT (Table 3). However, in multivariate analyses, after adjustment for all other variables, only outdoor temperature, age, BMI, and diabetes status remained significant independent determinants of the prevalence of $^{18}$F-FDG BAT (Table 3). The probability of detecting BAT decreased with increasing age ($P < 0.0001$; Table 3) and increasing BMI ($P < 0.0001$; Fig. 1B). In addition, the probability of seeing $^{18}$F-FDG BAT decreased with increasing outdoor temperature on the day of the scan ($P < 0.0001$; Fig. 1C). For each 1 C increase in mean outdoor temperature, the probability of perceiving $^{18}$F-FDG BAT decreased by 0.12%. The highest probability of observing $^{18}$F-FDG BAT was in February, whereas the lowest probability was in July (Supplemental Fig. 2). Moreover, the probability of detecting $^{18}$F-FDG BAT was associated with the season ($P = 0.04$), which was higher in winter than spring ($P = 0.005$) and tended to be higher in winter compared with summer and autumn ($P = 0.06$ and $P = 0.09$, respectively). The probability of having

**TABLE 2.** Distribution patterns in patients with $^{18}$F-FDG uptake[a]

| Pattern | Cervical/ supraclavicular | Paravertebral | Mediastinal | Perirenal | Patients with $^{18}$F-FDG uptake (%) |
|---|---|---|---|---|---|
| 1 | ▮ | | | | 33.5 |
| 2 | ▮ | ▮ | | | 29.6 |
| 3 | ▮ | ▮ | ▮ | | 11.0 |
| 4 | ▮ | ▮ | ▮ | ▮ | 11.9 |
| 5 | | ▮ | | | 3.0 |
| 6 | ▮ | | ▮ | | 1.8 |
| 7 | ▮ | | | ▮ | 1.8 |
| 8 | ▮ | ▮ | | ▮ | 3.4 |
| 9 | | ▮ | ▮ | ▮ | 1.2 |
| 10 | | ▮ | | ▮ | 0.6 |
| 11 | ▮ | | ▮ | ▮ | 1.2 |
| 12 | | ▮ | ▮ | | 0.9 |
| Patients with $^{18}$F-FDG uptake (%) | 94.2 | 61.6 | 28.0 | 20.1 | |

[a] ▮ Indicates the presence of $^{18}$F-FDG uptake in this depot.

**TABLE 3.** Determinants of the prevalence, mass, and glucose-uptake activity of detected BAT in $^{18}$F-FDG PET/CT scans

| | Prevalence[a] | | Mass[b] | | | Activity[b] | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis | | Univariate analysis | Multivariate analysis | |
| Variable | *P* value | *P* value | *P* value | Slope | *P* value | *P* value | Slope | *P* value |
| Sex (male *vs.* female) | <0.0001 | 0.80 | <0.0001 | −72.6 | <0.0001 | <0.0001 | −203.6 | <0.0001 |
| Age | <0.0001 | <0.0001 | <0.0001 | −1.7 | <0.0001 | <0.0001 | −4.9 | <0.0001 |
| Age × sex | 0.004 | 0.004 | — | — | — | — | — | — |
| BMI | <0.0001 | <0.0001 | <0.0001 | −2.7 | <0.0001 | <0.0001 | −7.6 | <0.0001 |
| Lean body weight | <0.0001 | 0.57 | <0.0001 | — | 0.90 | <0.0001 | — | 0.85 |
| Diabetes (yes *vs.* no) | <0.0001 | 0.0003 | <0.0001 | −59.7 | 0.0002 | <0.0001 | −168.6 | 0.0002 |
| Plasma glucose level | <0.0001 | 0.95 | <0.0001 | — | 0.74 | <0.0001 | — | 0.72 |
| Outdoor temperature[c] | <0.0001 | <0.0001 | <0.0001 | −1.5 | <0.0001 | <0.0001 | −4.1 | <0.0001 |
| Day length | 0.002 | 0.80 | 0.0007 | — | 0.17 | 0.0007 | — | 0.19 |
| Season | 0.07 | 0.04 | 0.03 | — | 0.04 | 0.02 | — | 0.36 |
| Cancer (active *vs.* no cancer) | 0.57 | 0.86 | 0.23 | — | 0.99 | 0.24 | — | 0.98 |

[a] Analyses were done by logistic regression.

[b] Analyses were done with the Tobit model.

[c] Temperature on the day of the scan.

$^{18}$F-FDG BAT was 4 times higher in nondiabetic than in diabetic patients ($P = 0.0003$; Fig. 1D). In the multivariate model, sex was no longer an independent determinant of the prevalence of $^{18}$F-FDG-detected BAT. Nonetheless, a significant interaction between sex and age was observed ($P = 0.004$); the likelihood of having $^{18}$F-FDG BAT was higher in women than men, with the difference diminishing with age (Fig. 1A).

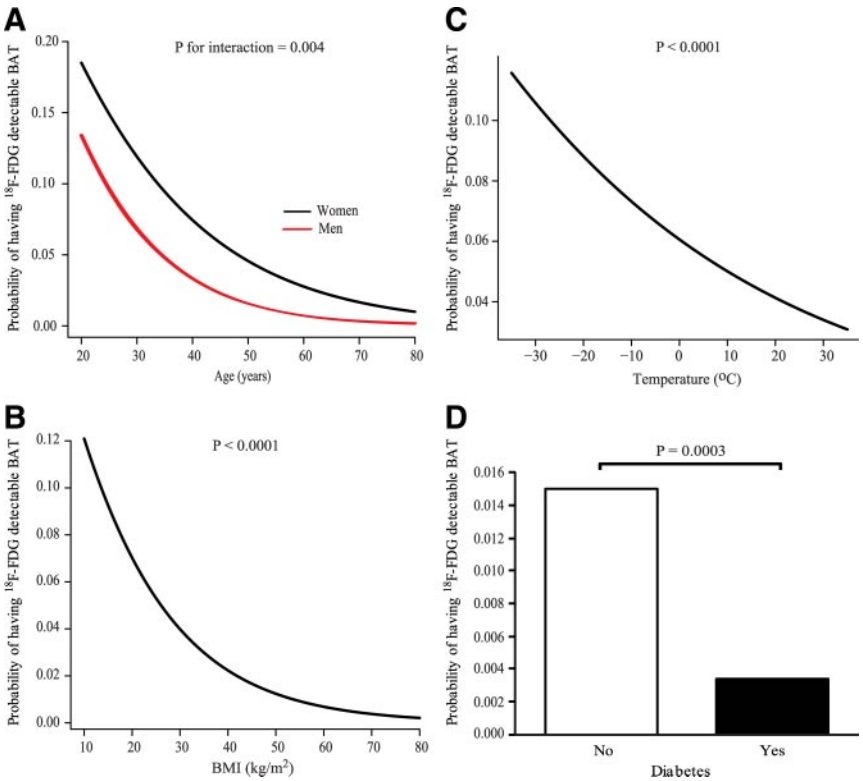


**FIG. 1.** Prevalence of $^{18}$F-FDG-detected BAT in function of age and sex (A), BMI (B), outdoor temperature (C), and diabetes status (D) as assessed with a multivariate logistic regression analysis.

## Determinants of $^{18}$F-FDG BAT distribution patterns

When examining the four most frequent distribution patterns (Table 2), we observed negative associations between the probability of having one of the patterns and outdoor temperature ($P = 0.0001$; Fig. 2D), BMI ($P < 0.0001$; Fig. 2C), and diabetes status ($P = 0.0002$). We also observed a significant interaction between sex and age ($P = 0.003$; Fig. 2, A and B), with the sex difference decreasing with advancing age. The probability of detecting cervical/supraclavicular only or cervical/supraclavicular plus paravertebral $^{18}$F-FDG BAT decreased with increasing outdoor temperature, increasing age, and increasing BMI. Of note, the probability of detecting three depots (cervical/supraclavicular, paravertebral, and mediastinal) or all four depots remained fairly constant with age, BMI, and outdoor temperature.

## Determinants of the mass and glucose-uptake activity of $^{18}$F-FDG BAT

$^{18}$F-FDG-detected BAT mass was lower in men than women ($P < 0.0001$; Table 3). BAT mass decreased with increasing age ($P < 0.0001$), increasing BMI ($P < 0.0001$), and increasing outdoor temperature ($P < 0.0001$). For every 1-U increase in age, BMI, and outdoor temperature, the mass of $^{18}$F-FDG BAT decreased by 1.7, 2.7, and 1.5 g, respectively. Season also influenced BAT mass

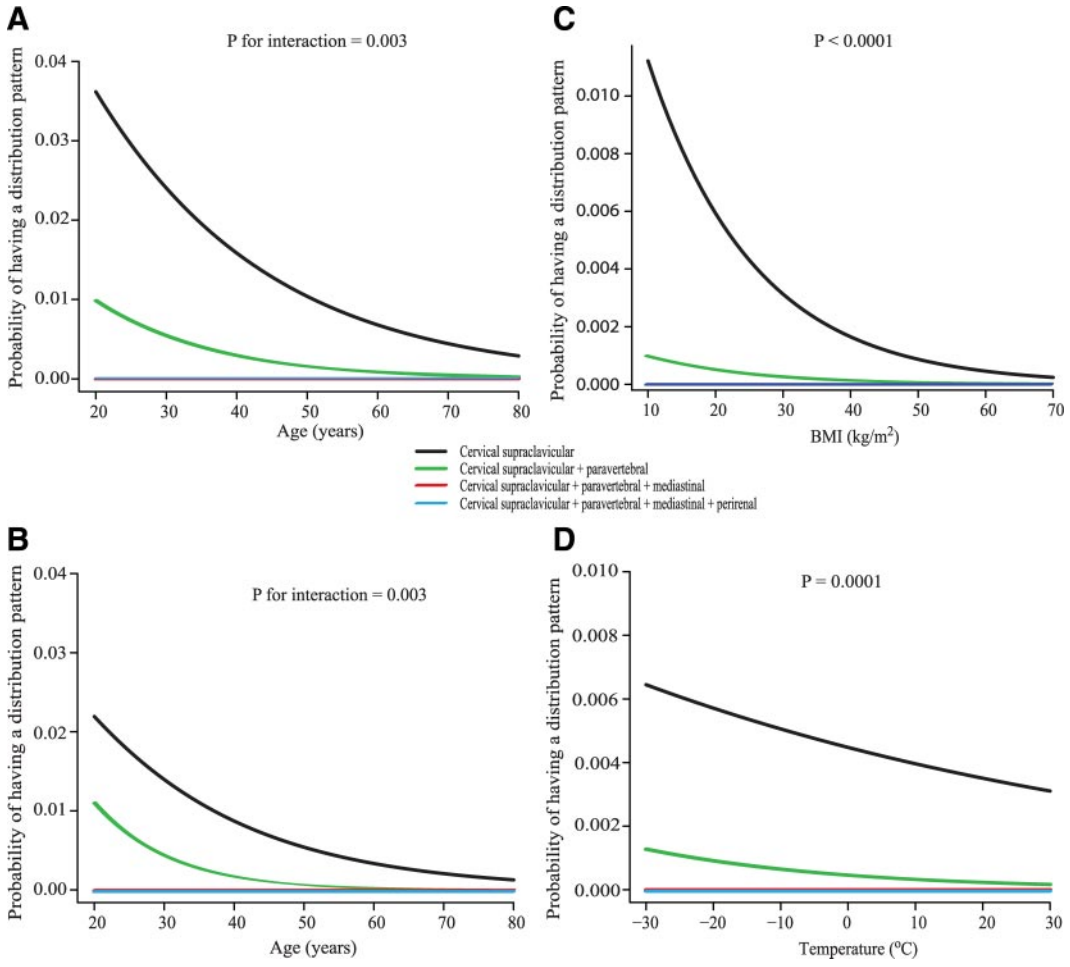


**FIG. 2.** Pattern of distribution of $^{18}$F-FDG-detected BAT in function of age in women (A), age in men (B), BMI (C), and outdoor temperature (D) as assessed with the Tobit model.

($P = 0.04$), which was significantly higher in winter than spring ($P = 0.01$). $^{18}$F-FDG-detected BAT mass also tended to be higher in winter compared with summer and autumn ($P = 0.10$ and $P = 0.06$, respectively). Finally, nondiabetic patients had a higher BAT mass than diabetic patients ($P = 0.0002$).

Regarding the glucose-uptake activity of $^{18}$F-FDG-detected BAT, a higher glucose-uptake activity was associated with lower outdoor temperature, female sex, younger age, lower BMI, and nondiabetic status (Table 3). The glucose-uptake activity of $^{18}$F-FDG-detected BAT decreased by 7.6 g × SUV for every increase of 1 kg/m$^2$ in BMI. There was a significant correlation between the mass and glucose-uptake activity of $^{18}$F-FDG-detected BAT ($r = 0.99$, $P < 0.0001$), indicating that individuals with the larger BAT mass were also the ones with the higher glucose-uptake activity.

### Determinants of the prevalence, mass, and glucose-uptake activity of $^{18}$F-FDG-detected BAT in subjects scanned during winter

Because exposure to colder temperatures at the time of the PET/CT examinations seems to be a critical factor determining $^{18}$F-FDG BAT prevalence independently of the season, we investigated whether the prevalence, mass, and glucose-uptake activity of $^{18}$F-FDG-detected BAT were affected differently during winter, *i.e.* during the season showing BAT's highest stimulation. We still observed a negative association between the prevalence of $^{18}$F-FDG BAT and age ($P < 0.0001$) and BMI ($P = 0.002$). We also observed that women had a higher prevalence of $^{18}$F-FDG BAT than men ($P = 0.001$), and there was a strong tendency for nondiabetic subjects to have more frequent $^{18}$F-FDG BAT than diabetic subjects ($P = 0.059$). The same significant associations were found for mass and glucose-uptake activity of $^{18}$F-FDG-detected BAT (data not shown).

## Discussion

The present study was carried out to further disentangle the factors determining the prevalence, mass, and glucose-uptake activity of $^{18}$F-FDG-detected BAT in humans. This investigation was done on a large cohort of patients (n =

4842) and, to our knowledge, on the largest number of patients with $^{18}$F-FDG-detected BAT (n = 328) reported to date. We conclude that the prevalence, mass and glucose-uptake activity of $^{18}$F-FDG-detected BAT are determined by outdoor temperature, sex, age, BMI, and diabetes status. The influence of sex on $^{18}$F-FDG BAT prevalence appears to decline with age.

In this study, the observed prevalence of $^{18}$F-FDG BAT was 6.8%, which is consistent with the prevalence reported in several other studies involving large cohorts of patients (8, 13–15). It is clear that an observed prevalence of $^{18}$F-FDG BAT of approximately 5% represents an underestimation of the true prevalence of BAT (activated plus nonactivated). In fact, BAT needs to be metabolically active to take up $^{18}$F-FDG, and the conditions into which the $^{18}$F-FDG PET/CT scans are performed in most studies involving large cohorts of patients do not particularly favor induction of BAT metabolic activity. In the present study, our patients were neither warmed nor systematically cold stimulated. One has nonetheless to assume that the subjects who exhibited $^{18}$F-FDG BAT were under some activation (cold or other factors). Factors such as age, sex, BMI, and the diabetic status were all seen to be independent factors determining the prevalence, mass, and glucose-uptake activity of $^{18}$F-FDG-detected BAT. Whether those factors cause direct activation of BAT appears intuitively implausible; one has, however, to admit that those determinants could modulate BAT activation, be it due to cold or other factors stimulating BAT adrenergic activity.

Expectedly, we observed that low outdoor temperature was associated with increased prevalence, mass, and glucose-uptake activity of $^{18}$F-FDG-detected BAT. In addition, the prevalence and mass of $^{18}$F-FDG BAT tended to be higher during the winter than during other seasons, in agreement with previous reports (8, 12–14). Our results suggest that exposure to lower temperatures on the day of scan is more important than long-term exposure because the temperature on the day of the scan was a better predictor than the mean temperatures 2 d, 3 d, 7 d, and 1 month before the scan (data not shown). Importantly, patients were not warmed in the present study, even though warming of the subjects before $^{18}$F-FDG PET/CT was previously used to eliminate detection of $^{18}$F-FDG BAT (22). Cold would stimulate BAT activity via the sympathetic nervous system, which represents the ultimate physiological pathway to control BAT activity (4). In this regard, cervical/supraclavicular UCP1-positive cells are not only highly vascularized but also densely innervated with nerve fibers immunopositive for tyrosine hydroxylase, indicating a rich sympathetic innervation (11). Au-Yong *et al.* (13) suggested that photoperiod (night length), more than outdoor temperature, might be the key factor accounting for the season effect on BAT. In the present study, univariate analyses also showed a positive relationship between day length and the probability of having $^{18}$F-FDG BAT. However, the relationship was no longer significant in multivariate analyses, suggesting that the effect of day length was possibly confounded by the effect of outdoor temperature.

Confirming previous findings (8, 11, 12, 17, 18), we found that age determines the prevalence, mass, and glucose-uptake activity of $^{18}$F-FDG-detected BAT. Indeed, the prevalence, mass, and glucose-uptake activity of $^{18}$F-FDG BAT was higher in younger individuals than in older subjects. Furthermore, age appeared to be the most important factor determining the prevalence of $^{18}$F-FDG BAT, as also previously suggested by Pfannenberg *et al.* (18). Indeed, age was associated with the highest probability of detecting BAT (after adjustments for all other variables). The age effect was also significant in winter, further substantiating an age modulation of cold-induced BAT metabolic activity. In agreement with this, Saito *et al.* (12) reported a prevalence of cold-induced BAT $^{18}$F-FDG uptake of 52 and 8% in subjects aged 23–35 yr and subjects aged 38–65 yr, respectively. Furthermore, Zingaretti *et al.* (11) reported that UCP1-positive subjects were younger (39 yr) than UCP1-negative subjects (55 yr). Rodent studies have also documented an age-related decline in nonshivering thermogenesis due to the presence of less functional BAT (23).

We observed that the prevalence of $^{18}$F-FDG BAT was higher in women than in men but that the difference disappeared with advanced age. Women also had a higher mass and glucose-uptake activity of $^{18}$F-FDG-detected BAT than men. A higher prevalence of $^{18}$F-FDG BAT in women has been frequently reported in human studies (8, 13–18). A sexual dimorphism in BAT thermogenesis has also been observed in animal studies. Under usual rodent housing temperature (22 C), female rats have been shown to have a greater thermogenic capacity (higher UCP1 content, total and mitochondrial protein content, and BAT size in relation to body weight) than male rats (24–27), differences suggested to be attributed to a lower threshold temperature for cold-induced thermogenesis in males (26). Whether women generally more often experience cold stress for a given temperature during the PET/CT examination cannot therefore be excluded. In animal studies, there are no more sex differences in thermogenic capacity/activity when male and female rats are exposed to cold (4 C) (26), supporting the hypothesis that women have a higher threshold to get cold stimulated. The latter finding is in agreement with the results of Saito *et al.* (12),

who did not report a sex difference when the subjects were exposed to cold.

Another factor that has been associated with a higher prevalence of $^{18}$F-FDG-detected BAT is leanness (9, 11, 12, 18). However, it has also been reported by some (8) that this association is restricted to individuals older than 64 yr, whereas others (18) have rather suggested that the association is only seen in younger men. In the present large cohort of patients, BMI was a determinant of the prevalence of activated BAT independent of age. We indeed found, after adjustment for all other variables, a negative association between BMI and the probability of detecting $^{18}$F-FDG BAT. The mass and glucose-uptake activity of $^{18}$F-FDG BAT also showed a negative association with BMI. That the prevalence, mass and glucose-uptake capacity of $^{18}$F-FDG BAT can be reduced with increasing BMI has been reported before, even in acutely cold exposed subjects (9). Interestingly, the sole subject who resisted cold-induced BAT $^{18}$F-FDG uptake in the study by van Marken Lichtenbelt *et al.* (9) was the individual displaying the largest BMI (38.7 kg/m$^2$) and percentage of body fat (41.8%). Similarly, the only two subjects with BAT $^{18}$F-FDG uptake sites in a subgroup of older subjects (38–65 yr) described by Saito *et al.* (12) were very lean with BMI of 22.2 and 20.6 kg/m$^2$.

Whether higher mass and glucose-uptake activity of $^{18}$F-FDG BAT can play a role in preventing obesity has yet to be proven. This is nonetheless an appealing possibility. Rothwell and Stock (28) about 3 decades ago suggested that 20% of total resting energy expenditure could be accounted for by 50 g of maximally stimulated BAT. In a recent study, Virtanen *et al.* (10) suggested that 63 g of fully activated BAT could burn approximately 4.1 kg of adipose tissue in a year. Our data indicate that on average (without systematic cold exposure), men and women can stimulate up to 24 and 42 g of BAT, respectively. That BAT thermogenesis can play a role in energy balance is certainly supported by animal data. Indeed, ablation of UCP1 in mice living at thermoneutrality (which most resembles human normal environment) leads to diet-induced obesity (29). Further studies addressing the role of BAT in energy metabolism in humans are warranted.

We also showed a higher prevalence, mass, and glucose-uptake activity of $^{18}$F-FDG BAT in nondiabetic than in diabetic patients. Noteworthily, glycemia was not independently associated with the prevalence, mass, and glucose-uptake activity of $^{18}$F-FDG BAT in the present study. Other studies have also shown no relationship between BAT and glycemia (8). Further studies are needed to determine whether lower BAT activity plays a role in type 2 diabetes causation or whether type 2 diabetes is responsible for lower BAT mass and activity. The reduced insulin signaling and UCP1 expression have been reported to favor brown adipocyte death *in vitro* (30), supporting a role for insulin resistance in reduced BAT activation. Taken together, the associations that we observed with diabetes status, age, and BMI point toward a possible independent effect of insulin sensitivity on BAT activity in humans. Unfortunately, we could not assess circulating insulin levels in the present cohort. Whether change in insulin sensitivity underlies all these associations needs further studies.

Data from the distribution patterns indicate that the cervical/supraclavicular and paravertebral depots are the most prevalent locations of $^{18}$F-FDG-detected BAT, which is in agreement with previous investigations (7–9). In addition, we observed that their prevalence is influenced by age, BMI, and outdoor temperature. Our results suggest that few individuals possess $^{18}$F-FDG BAT in all four locations, and the prevalence of mediastinal and perirenal $^{18}$F-FDG BAT is always accompanied by cervical/supraclavicular or paravertebral $^{18}$F-FDG BAT. Moreover, other factors than the one examined in this study seem to influence the prevalence of mediastinal and perirenal $^{18}$F-FDG BAT because the probability of having mediastinal and perirenal $^{18}$F-FDG BAT remained fairly constant with age, BMI, and outdoor temperature as opposed to cervical/supraclavicular and paravertebral depots.

Although the individuals examined in this study were patients undergoing PET/CT for cancer diagnosis or staging, it is unlikely that cancer was responsible for the prevalence of $^{18}$F-FDG-detected BAT. This is evidenced by the proportion of patients with active cancer, which was the same (~50%) in patients with and without $^{18}$F-FDG-detected BAT. Moreover, cancer status had no significant effect on the prevalence, mass, and glucose-uptake activity of $^{18}$F-FDG BAT in univariate as well as multivariate analyses.

In conclusion, the results of the present large cohort study showed that the main determinants of the prevalence, mass, and glucose-uptake activity of $^{18}$F-FDG-detected BAT are outdoor temperature, age, sex, BMI, and diabetes status. As tentatively illustrated in Supplemental Fig. 3, $^{18}$F-FDG uptake in BAT likely necessitates a sympathetic nervous system-mediated BAT activation driven by a cold stimulus or other BAT activators. Factors such as young age or chronic exposure to a cold environment (as it is likely to occur in winter) would enhance BAT capacity for thermogenesis (BAT mass, BAT mitochondria content, BAT UCP1 content). The larger the BAT capacity, the higher would be the $^{18}$F-FDG uptake upon a given activation. Low BMI or absence of diabetes (or other factors associated with those conditions) could also en-

hance BAT capacity. Having a higher temperature threshold than men, women would more readily respond to cold.

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