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Original article

Seasonal effects on resting energy expenditure are dependent on age and percent body fat

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SUMMARY

Seasonal variation in resting energy expenditure (REE) is still under debate. This study investigated seasonal changes in REE and relevant factors among Korean adults.

A total of 867 healthy volunteers (385 men and 482 women) aged 20–69 years were divided into four seasonal groups and subgroups based on age, body mass index (BMI), and percent body fat (PBF) quartiles. REE, body composition, glucose metabolism, thyroid hormones, and catecholamines were measured.

The seasonal factor contributed to REE independent of anthropometric indices, with additional variation decreasing from 6% to 2% among younger and older persons, respectively. The adjusted REE in the winter was 5.4–13.9%, 7.8–14.3%, and 8.6–11.9% higher than that in the summer in the age, BMI, and PBF subgroups, respectively. T3 and log-transformed norepinephrine (NE_{log}) were higher, whereas log-transformed epinephrine (EPI_{log}) was lower in the winter compared to the summer. The magnitude of the winter-summer difference in REE and T3 and of the summer-winter difference in EPI_{log} were reduced three-fold between the lowest and highest intervals of age and PBF, whereas the difference in NE_{log} was constant across all age and PBF intervals. There was no obvious change in seasonal differences in REE or its relevant biomarkers across BMI intervals.

In summary, season is an independent predictor of REE and its effect is attenuated by the increment of age and PBF but not BMI.

1. Introduction

An imbalance between energy intake and expenditure has been blamed for the emerging prevalence of obesity and its related health issues worldwide [1,2]. In humans, the energy expenditure (EE) required for maintaining vital body functions at rest accounts for the largest proportion (60–80%) of the total EE and is defined as resting energy expenditure (REE). Because of its important role, REE has been widely used in research on energy metabolism and clinical practice, such as weight-control interventions [3]. The gold standard method to measure REE is employing indirect calorimetry that collects information on respiratory exchange – oxygen consumption (VO_2) and carbon dioxide production (VCO_2) – from the breath of an individual at resting state and then indirectly estimates the EE equivalent [4]. However, because this accurate measurement is relatively complicated and due to its high costs when applied to large-scale epidemiological studies or long-term intervention assessment, numerous anthropometric-based estimations of REE have been developed. Since the first REE equations were introduced by Harris and Benedict in 1919, hundreds of REE equations have been constructed, mostly using age, sex, weight, height, lean body mass (LBM), and percent body fat (PBF) as predictors [5–7]. Unfortunately, the predictive power of these equations varies broadly with the determinant of coefficients ranging from 0.69 to 0.84, and is dependent on age, sex, body mass index (BMI), and body composition [6–8]. Very few studies have examined the effect of environmental temperature on predicting REE.

Although EE at rest is strongly determined by body size and body composition, especially LBM, REE measurement is also influenced by the thermoregulation process that is closely associated with ambient temperature and the acclimation of each individual [9]. In a cold environment, the human body requires more

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EE in the thermoregulation process to produce heat generated for warming [10]. The increase in cold-induced heat production originates from a rise in food intake, non-exercise, shivering, and non-shivering thermogenesis (NST) [11]. During acclimation to a cold environment, brown adipose tissue (BAT) is activated and promotes mitochondrial uncoupling to initiate NST, the most important process for long-term cold adaptation [11,12]. Cold-induced NST is regulated through a complex network via the sympathetic nervous system (SNS), the thyroid hormone axis (especially due to the role of T3), and the catecholamine signaling pathway (e.g., norepinephrine [NE]) [12]. However, whether human REE substantially elevates during the cold season after controlling all potential influential factors remains under debate. Several studies have revealed a significant increase in REE in the winter compared with the summer [13–15], whereas others have found no difference [16,17]. A longitudinal study measured sleeping EE (SEE) in 25 volunteers and found that the seasonal factor accounted for 17% variation in SEE [13], whereas a cross-sectional study on a relatively large population revealed no difference in REE measured in winter and summer [16]. This discrepancy may be due to the fact that the former employed a small sample size with lean, young volunteers aged younger than 30 years, whereas the latter was based on overweight, middle-aged individuals. We, therefore, assume that the seasonal effect on REE differs according to age and/or body composition factors, such as BMI and PBF.

Thus, this study investigated (i) the variation of REE and its relevant factors, such as body composition, thyroid function, and catecholamine signals, across four seasons and (ii) the effect of age and body composition on the variation of REE across four seasons in a large-scale Korean population.

2. Methods

2.1. Participants

A total of 1082 apparently healthy volunteers (465 men and 617 women) aged 20–69 years were recruited between 2009 and 2017 through advertisements by the Asan Medical Center (AMC) in Seoul, the capital city of the Republic of Korea. Potential participants were excluded if they had type II diabetes mellitus confirmed by disease history and/or fasting plasma glucose (FPG) ≥126 mg/dL or a plasma glucose level after a 2-h oral glucose tolerance test (2h-OGTT) ≥200 mg/dL (n = 48) and/or hypothyroidism (TSH >4.1 mIU/mL and T4 <0.7 μg/dL, n = 52) and/or hyperthyroidism (TSH <0.4 mIU/mL and T4 >1.8 μg/dL, n = 1), to eliminate any bias in REE measurement induced by metabolic disorders [18,19]. To confirm the validity of REE measurements, potential participants were also excluded if they had REE measurements with a respiratory quotient (RQ) < 0.67 (n = 99) or ≥1.3 (n = 3) [20]. We also excluded those with missing FPG, 2h-OGTT, and thyroid function test data (n = 38). Finally, a total of 867 participants (385 men and 482 women) were included in the analysis. Participants were divided into seasonal groups, including Spring (n = 330, enrolled in March, April, and May), Summer (n = 148, enrolled in June, July, and August), Fall (n = 220, enrolled in September, October, and November), and Winter (n = 169, enrolled in December, January, and February) (Supplementary S1). The mean temperatures of the four seasons in Seoul from 2009–2017 were 12.3 ± 5.6, 25.1 ± 1.6, 15.0 ± 6.2, and −1.11 ± 2.31 degrees Celsius for the spring, summer, fall, and winter, respectively [21] (Supplementary S2). The study was approved by the Institutional Review Board of the AMC (IRB number: 2009-0722, 2012-0910, 2015-1263, 2017-0194) and informed consent was obtained from all participants.

2.2. REE measurement

REE was measured using an indirect calorimeter with a ventilated hood system (Vmax ENCORE 29c Sensormedic, Viasys Healthcare, Yorba Linda, CA, USA). Calibration with standard gases and a standard volume was performed daily in the morning before the measurement following the manufacturer's instructions. Only stable measurements with a coefficient of variation <10% were collected for REE calculation. Participants were asked to maintain a fasting state after the last dinner, to avoid vigorous physical exercise and alcoholic beverages during the previous 24 h, and to refrain from stimulants such as smoking or caffeinated drinks 6 h before measurement. The REE measurement was performed over a period of 20 min while the participant remained lying on a bed in supine posture awake without reading or listening activities in a thermoneutral environment. Room temperature was set up between 22 and 25 °C. The VO_2 (mL/min) and VCO_2 (mL/min) were collected in a sealed ventilated hood that was connected to the system. The measured REE (mREE) then was calculated using the revised Weir equation for each RQ range [22]:

$$\text{mREE (kcal/day)} = 4.2 \times 1.44 \times VO_2 + 0.494 \times 1.44 \times VCO_2 \text{ if RQ} \leq 0.7; \quad (1)$$

$$\text{mREE (kcal/day)} = 3.94 \times 1.44 \times VO_2 + 1.106 \times 1.44 \times VCO_2 \text{ if RQ} > 0.7 \text{ and RQ} < 1; \quad (2)$$

and

$$\text{mREE (kcal/day)} = 3.677 \times 1.44 \times VO_2 + 1.342 \times 1.44 \times VCO_2 \text{ if RQ} > 1 \quad (3)$$

Carbohydrate oxidation (C-oxidation, g/min) and lipid oxidation (L-oxidation, g/min) were calculated using the Frayn equation (Eqs. (4) and (5)) [23]. Predicted REE (pREE) was calculated using the Harris-Benedict revised equation using age, body weight (BW), and height (Eqs. (6) and (7)) [24], whereas metabolic status was categorized by the mREE-to-pREE ratio in which hypo-, normo-, and hypermetabolism were in the range of <90%, 90–110%, and >110% of the mREE-to-pREE ratio, respectively [25].

$$\text{C}-\text{oxidation (kg/min)} = 4.12 \times VCO_2/1000 - 2.91 \times VO_2/1000 \quad (4)$$

$$\text{L}-\text{oxidation (kg/min)} = 1.69 \times VO_2/1000 - 1.69 \times VCO_2/1000 \quad (5)$$

$$\text{pREE (kcal/day)} = 88.362 + 13.397 \times \text{BW} + 4.799 \times \text{Height} - 5.677 \times \text{Age (for men)} \quad (6)$$

$$\text{pREE (kcal/day)} = 447.593 + 9.274 \times \text{BW} + 3.098 \times \text{Height} - 4.330 \times \text{Age (for women)} \quad (7)$$

2.3. Body composition

BW and height were measured using a digital scale to the nearest 0.1 kg. Body composition was measured by a multi-frequency bioelectrical impedance analyzer (MF-BIA) with an eight-polar tactile-electrodes impedance-meter (InBody 720, Biospace, Seoul, Korea). This device employs six electronic frequencies of 1, 5, 50, 250, 500, and 1000 kHz for segmental and total impedance assessment that is used to estimate total body water (TBW). LBM (in kg) was estimated from TBW and

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anthropometrics with an algorithm for the Asian population. Body fat mass (BFM) (in kg) and PBF (%) were estimated by subtracting LBM from BW and $\left(\frac{BFM}{BW}\right) \times 100$, respectively.

2.4. Blood assay

The baseline blood assay included FPG (mg/dL), insulin (mU/mL), thyroid hormones (T3, T4, and TSH), and stress-related hormones (cortisol, epinephrine, and NE). Plasma glucose concentration was measured using the glucose oxidase technique (Beckman, Fullerton, CA, USA). Thyroid hormones and insulin concentration were measured by an electrochemiluminescence immunoassay (ECLIA, Roche, Germany). Plasma cortisol concentration was measured by a radioimmunoassay (Cortisol RIA CT, AMP, Germany), and epinephrine and NE were measured using high-performance liquid chromatography (plasma catecholamine, Bio-Rad, Germany). An OGTT was performed according to a standard protocol [26]. Insulin resistance (HOMA-IR) was calculated using Eq. (8) [27]:

$$\text{HOMA} - \text{IR} = \frac{\text{insulin} \times \text{FPG}}{22.5} \quad (8)$$

where insulin and FPG are measured in mU/L and mmol/L, respectively. Blood sampling was done before the REE measurement.

2.5. Data analysis

Statistical analysis was performed using R program version 3.3.2 on the Windows 7 platform. Highly skewed variables, including insulin, HOMA-IR, cortisol, epinephrine, and NE, were log-transformed before further analysis. One-way analysis of variance (ANOVA) was used to test the hypothesis that the mean values of continuous variables among seasonal groups are the same. The comparison of mean differences after adjusting for age, sex, LBM, and PBF was performed by analysis of covariance (ANCOVA), in which the Summer group was used as the reference. To compare the magnitude of differences in the ANCOVA test, all independent variables were scaled to mean as zero (z-score transformation). The chi-square test was used to test the hypothesis that the proportions of metabolic status would be identical across seasonal groups. ANOVA and chi-square tests were analyzed for men and women separately. To estimate the 95% confidence interval (CI) of effect size (R^2) in univariate and multivariate regression predictive models for mREE across seasonal groups, bootstrapping was applied with 1000 repetitions. To assess the influence of age, BMI, and PBF in seasonal effects on REE change, sub-analyses were performed separately for four age intervals and for BMI and PBF quartiles. Interaction terms in predicting REE between the seasonal factor (Winter versus Summer) and age, PBF, and BMI were analyzed by multiple regression analysis on the whole dataset and on men and women separately. Significance was set at a p value < 0.05.

3. Results

3.1. REE measurement

Participants in the four seasonal groups did not differ in anthropometric characteristics, including age, BMI, BSA, LBM, BFM, and PBF, in the gender-specific analysis (Table 1). A significant difference was observed in mREE and its relevant factors across seasonal groups (all p-values <0.001). mREE, mREE per BW, mREE per LBM, and the mREE-to-pREE ratio were the lowest in the Summer group, increased gradually in the Spring and Fall groups, and were the highest in the Winter group in both men and women. On average, mREE in the Winter group elevated 164 kcal/d (11.3%) and 108 kcal/d (9.6%) compared with the Summer group in men and women, respectively (Table 1). After adjusting for age, sex, LBM, and PBF, ANCOVA revealed the same trend: the average differences in z-score of mREE, mREE per BW, mREE per LBM, and the mREE-to-pREE ratio of the Spring, Fall, and Winter groups were significantly higher than the Summer group (Fig. 1). The addition of room temperature into the model slightly increased the seasonal effect on REE (data not shown). The prevalence of hypometabolism was the highest in the Summer group (73.1% and 61.7% in men and women, respectively), whereas the prevalence of normometabolism was the highest in the Winter group (76.5% and 69.3% in men and women, respectively) (Table 2). C-oxidation did not differ across seasonal groups in absolute and adjusted values, whereas L-oxidation was higher in the Winter and Spring groups than in the Summer group (Table 1 and Fig. 1).

Figure 2(A-C) shows the ΔmREE of each season using the Summer group as the reference after adjusting for age, sex, LBM, and PBF in each group of age interval and BMI and PBF quartiles. All mREEs were significantly lower in the Summer group. However, the magnitude of this difference was attenuated in the higher age increments, especially in the comparison between the Summer and Winter groups. The mean and 95% CI of difference in the adjusted mREE between the Winter and Summer groups was 182.1 (117.3–247.0) kcal/d (13.9%) and 62.8 (15.3–110.3) kcal/d (5.4%) in those aged 20–29 years and 50–68 years, respectively. The same trend was observed in the subgroup analysis for PBF quartile: the higher the PBF quartile, the lower the magnitude of difference in mREE between the Summer and Winter groups. The mean and 95% CI of difference in the adjusted mREE between the Winter and Summer groups was 198.7 (132.9–264.5) kcal/d (14.3%) and 91.2 (41.1–141.2) kcal/d (7.8%) in those with a PBF of 7.6–20.8% and 31.3–45.4%, respectively. On the contrary, the higher the BMI quartile, the higher magnitude of difference in mREE between the Summer and Winter groups. The mean and 95% CI of difference in the adjusted mREE between the Winter and Summer groups was 97.8 (43.9–151.6) kcal/d (8.6%) and 168.0 (106.1–229.9) kcal/d (11.9%) in those with a BMI of 16.4–20.9 kg/m^2 and those with a BMI of 24.9–34.8 kg/m^2, respectively.

Bootstrapping for regression analysis revealed that LBM is the most important factor among the anthropometric variables in the estimation of mREE. LBM, sex, PBF, age, and seasonal factor accounted for 64.3%, 46.2%, 10.7%, 5.3%, and 3.3% variation of mREE, respectively. The model that included age, sex, LBM, and PBF was able to explain 66.6% of the variation (Table 3-Model 5). Adding the seasonal factor to Model 5 increased the explained variation to 70.0% (Table 3-Model 7). Anthropometric factors were associated with a higher mREE in the Summer and Winter groups than in the Spring and Fall groups. On average, LBM was able to explain 77.2%, 75.3%, 60.0%, and 64.3% variation of mREE in the Summer, Winter, Spring, and Fall groups, respectively (Table 3-Model 3). The same trend was observed in the model using age, sex, LBM, and PBF as predictors.

In age-interval and PBF-quartile subgroup analyses, adding the seasonal factor to the model using anthropometric-based predictors increased the explained variation of mREE more in the younger and lower PBF groups than in the older and higher PBF groups (5.8% versus 1.8% for those aged 20–29 years and 50–68 years, respectively, and 7.8% versus 3.1% for those with a PBF between 7.6 and 20.8% and between 31.3 and 45.4%, respectively). On the contrary, the BMI had a weaker effect on the contribution of the seasonal factor in the lower BMI groups compared with the higher BMI groups (3.7% versus 5.5% in the lowest and highest BMI

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Table 1
Characteristics of participants stratified by gender.

	Summer	Spring	Fall	Winter	*p*
Men					
n	67	146	91	81	
Age (yrs)	34.48 (9.84)	37.41 (12.11)	36.35 (8.45)	38.73 (10.54)	0.093
mREE (kcal/d)	1445.34 (169.27)	1497.84 (188.23)	1569.59 (251.61)	1608.96 (187.46)	<0.001
mREE_per_BW (kcal/d/kg)	20.31 (2.23)	21.32 (2.63)	21.53 (2.71)	22.80 (2.64)	<0.001
mREE_per_LBM (kcal/d/kg)	25.57 (2.26)	27.03 (3.09)	27.56 (3.28)	28.79 (2.38)	<0.001
mREE_pREE (%)	85.78 (7.38)	90.92 (9.56)	92.50 (10.97)	97.71 (8.88)	<0.001
C-oxidation (g/min)	0.064 (0.047)	0.064 (0.066)	0.071 (0.057)	0.059 (0.069)	0.635
L-oxidation (g/min)	0.080 (0.022)	0.084 (0.031)	0.086 (0.026)	0.095 (0.034)	0.019
Respiratory quotient	0.775 (0.051)	0.775 (0.069)	0.776 (0.055)	0.766 (0.069)	0.685
BMI (kg/m^2)	23.79 (3.03)	23.76 (2.73)	24.28 (2.91)	23.82 (2.62)	0.523
BSA (m^2)	1.86 (0.17)	1.84 (0.15)	1.88 (0.15)	1.84 (0.13)	0.280
BFM (kg)	15.18 (5.92)	15.16 (5.48)	16.27 (6.74)	15.09 (5.59)	0.466
LBM (kg)	56.79 (6.93)	55.69 (6.37)	56.97 (6.06)	55.97 (5.75)	0.395
PBF (%)	20.53 (5.64)	20.98 (5.70)	21.69 (6.49)	20.84 (6.03)	0.646
FPG (mg/dL)	93.04 (9.30)	94.17 (8.12)	95.03 (9.14)	96.33 (9.41)	0.129
2h-Glucose (mg/dL)	107.62 (29.80)	105.35 (26.60)	103.99 (26.84)	101.65 (25.17)	0.579
Insulin_log	1.87 (0.67)	1.73 (0.60)	1.77 (0.56)	1.69 (0.66)	0.333
HOMA-IR_log	0.39 (0.71)	0.27 (0.63)	0.32 (0.59)	0.25 (0.68)	0.519
T3 (ng/mL)	1.10 (0.17)	1.21 (0.28)	1.19 (0.21)	1.27 (0.22)	<0.001
T4 (μg/dL)	7.24 (1.12)	7.39 (1.41)	7.64 (1.25)	7.54 (1.34)	0.234
TSH (mIU/mL)	1.80 (1.33)	2.07 (1.43)	2.08 (1.26)	1.86 (0.95)	0.349
Cortisol_log	2.67 (0.46)	2.56 (0.46)	2.61 (0.45)	2.57 (0.39)	0.371
Epinephrine_log	3.85 (0.54)	3.67 (0.79)	3.67 (0.59)	3.36 (0.80)	<0.001
Norepinephrine_log	5.37 (0.60)	5.50 (0.60)	5.43 (0.66)	5.75 (0.62)	0.001
Women					
n	81	184	129	88	
Age (yrs)	41.31 (13.12)	39.10 (10.76)	37.89 (9.02)	39.69 (10.49)	0.156
mREE (kcal/d)	1128.92 (115.41)	1199.92 (151.85)	1206.56 (156.44)	1236.25 (143.92)	<0.001
mREE_per_BW (kcal/d/kg)	19.74 (2.12)	21.26 (2.59)	21.84 (2.90)	21.80 (2.44)	<0.001
mREE_per_LBM (kcal/d/kg)	28.90 (2.54)	30.31 (3.31)	30.90 (3.66)	31.26 (3.23)	<0.001
mREE_pREE (%)	87.13 (6.58)	92.28 (9.65)	93.13 (10.03)	95.28 (8.91)	<0.001
C-oxidation (g/min)	0.043 (0.044)	0.046 (0.049)	0.051 (0.041)	0.046 (0.054)	0.716
L-oxidation (g/min)	0.065 (0.018)	0.070 (0.022)	0.068 (0.018)	0.073 (0.026)	0.144
Respiratory quotient	0.766 (0.062)	0.766 (0.064)	0.771 (0.051)	0.766 (0.068)	0.897
BMI (kg/m^2)	22.79 (3.06)	22.22 (2.77)	21.77 (2.98)	22.42 (2.41)	0.074
BSA (m^2)	1.60 (0.14)	1.59 (0.11)	1.57 (0.12)	1.59 (0.09)	0.503
BFM (kg)	18.56 (5.71)	17.17 (5.10)	16.58 (5.43)	17.29 (4.48)	0.064
LBM (kg)	39.27 (4.54)	39.72 (4.00)	39.24 (4.36)	39.66 (3.71)	0.705
PBF (%)	31.55 (5.79)	29.73 (5.65)	29.17 (6.22)	30.08 (5.69)	0.034
FPG (mg/dL)	90.54 (8.68)	89.75 (9.73)	92.02 (8.91)	89.61 (8.42)	0.130
2h-Glucose (mg/dL)	114.16 (28.67)	104.97 (25.22)	107.54 (25.04)	103.28 (24.78)	0.026
Insulin_log	1.85 (0.54)	1.63 (0.66)	1.76 (0.52)	1.68 (0.72)	0.037
HOMA-IR_log	0.35 (0.59)	0.11 (0.70)	0.27 (0.55)	0.17 (0.76)	0.029
T3 (ng/mL)	1.08 (0.16)	1.13 (0.23)	1.06 (0.20)	1.17 (0.24)	<0.001
T4 (μg/dL)	7.30 (1.06)	7.51 (1.23)	7.08 (1.33)	7.20 (1.21)	0.019
TSH (mIU/mL)	1.97 (1.15)	2.15 (1.26)	1.96 (1.16)	2.34 (1.24)	0.097
Cortisol_log	2.31 (0.41)	2.36 (0.49)	2.34 (0.42)	2.38 (0.42)	0.810
Epinephrine_log	3.60 (0.72)	3.49 (0.84)	3.43 (0.57)	3.26 (0.73)	0.020
Norepinephrine_log	5.37 (0.47)	5.56 (0.54)	5.23 (0.62)	5.58 (0.76)	<0.001

Data are presented as the mean (±standard deviation [SD]). mREE, measured resting energy expenditure; mREE_per_BW, mREE normalized for body weight; mREE_per_LBM, mREE normalized for lean body mass; mREE_pREE, proportion of mREE versus REE calculated by the Harris-Benedict equation; C-oxidation and L-oxidation, carbohydrate and lipid oxidation, respectively; BMI, body mass index; BSA, body surface area; BFM, body fat mass; LBM, lean body mass; PBF, percent body fat; FPG, plasma glucose at baseline; 2h-Glucose, plasma glucose after a 2-h oral glucose tolerance test; insulin, plasma insulin at baseline; HOMA-IR, insulin resistance; log, log transformed value.

quartiles, respectively) (Table 4). In multiple linear regression analysis, the interaction terms between seasonal factor and age was significant on the whole dataset ($p < 0.001$) and in the gender-specific analysis ($p = 0.012$ and 0.021 in men and women, respectively), whereas the interaction terms between seasonal factor and PBF was significant on the whole dataset only ($p < 0.001$), and the interaction terms between seasonal factor and BMI was not significant in any analysis (Supplementary S3 and S4).

3.2. Metabolic-related factors

Several metabolic-related factors were examined, including glucose metabolism, thyroid hormones, and plasma catecholamines. Figure 1 shows that after adjusting for age, sex, LBM, and PBF, the Winter group had higher T3 and log-transformed NE levels and lower 2h-OGTT glucose, plasma insulin, HOMA-IR levels, and log-transformed epinephrine levels than the Summer group (all $p < 0.05$). This trend was also observed in the Spring and Fall groups, albeit at a lower magnitude. No differences were observed in T4, TSH, or plasma cortisol concentration.

In age-interval subgroup analysis, the difference in T3 between the Winter and Summer groups was substantially reduced as age increased (mean and 95% CI were 0.289 (0.196–0.381) and 0.004 (−0.076 to 0.083) in ng/mL for those aged 20–29 years and 50–68 years, respectively) (Fig. 2D). This trend was also observed in BMI- and PBF-quartile subgroup analyses, albeit at a lower magnitude (Fig. 2E and F). The magnitude of difference in log-transformed NE between the Winter and Summer groups did not differ across age intervals and PBF quartiles (Fig. 2M and O), whereas the magnitude of difference in log-transformed epinephrine between the Winter

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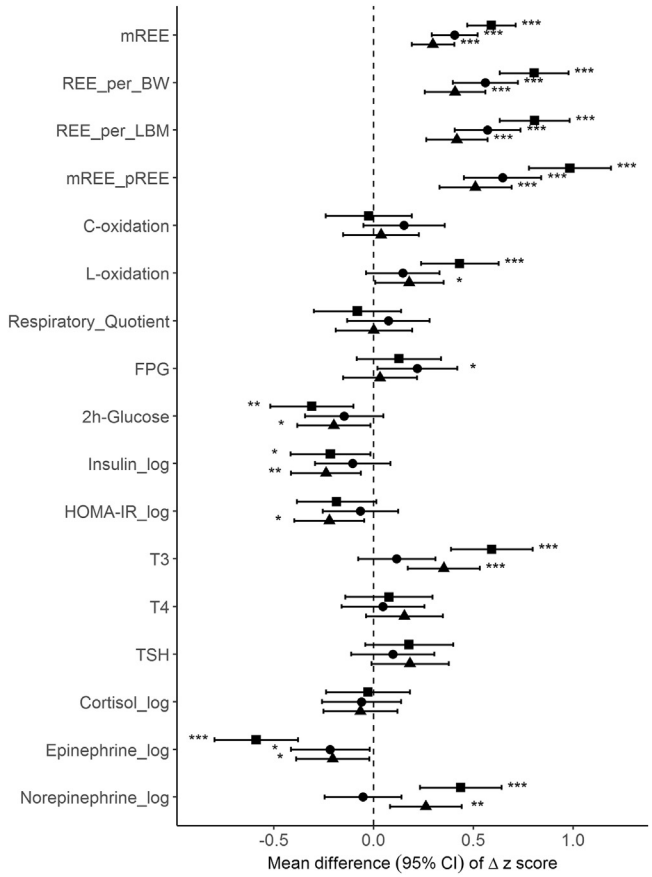

Fig. 1. Differences in the z-score of REE and relevant biomarkers across seasons after adjusting for age, gender, lean body mass, and percent body fat. ANCOVA was performed using the Summer group as the reference. Significance level: *, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$. Abbreviations: see Table 1. Data are shown as the mean difference and 95% confidence interval of the z-score. ■Solid square, ●solid circle, and ▲solid triangle represent Winter, Fall, and Spring groups, respectively.

and Summer groups increased from the lowest to the highest age intervals (Fig. 2G).

4. Discussion

There have been several attempts to develop a precise predictive equation for REE using anthropometric characteristics. However, the predictive power of these models is not consistently high [6,7]. One of the most crucial factors that may influence REE is the metabolic acclimation during four seasons, although this has not been investigated in detail. In this study, we found that (i) seasonal factor contributes substantially to the variation of REE independently of anthropometric characteristics, (ii) the magnitude of the seasonal effect is reduced by the increase in age and PBF, and (iii) this trend may be in concordance with seasonal changes in thyroid function and catecholamine.

Studies on seasonal changes in REE have yielded contradictory results [13–16]. This discrepancy may be due to differences in race, age, body composition, and/or sample size. A strong seasonal effect was observed in a lean and young population [13], whereas a study based on a middle-aged and high BMI population found no significant effect [16]. The current study enrolled a relatively large sample size with a wide range of age, BMI, and PBF. The adjusted mean of mREE was lowest in the Summer group, increased gradually in the Spring and Fall groups, and was the highest in the Winter group. Compared with the Harris-Benedict equation, the proportion of hypometabolism was the highest in the Summer group, whereas the proportion of normometabolism was the highest in the Winter group. This result suggests that the Harris-Benedict equation overestimated REE in a large number of individuals, especially those in the Summer group. This pattern may partially induce differences in the predictive power of anthropometric-based calculations of REE [6,7], although the studies enrolled participants in different seasons. Recent evidence indicates that skeletal muscle plays an important role in facultative thermogenesis in humans [12]. Uncoupling protein 3 (UCP3), a mediator of NST, and the β3-adrenoceptor that is related to the thermogenesis via SNS in humans, are mostly found in skeletal muscle [12]. Skeletal muscle is involved in the effect of T3 and catecholamines in facultative thermogenesis in humans [12,28]. Because skeletal muscle is a major part of LBM, these anthropometric factors are the strongest predictors in REE calculation. However, interestingly, we found that the contribution of anthropometric factors in predicting REE was higher in the Summer and Winter groups and lower in the Spring and Fall groups. Because the variation of mean temperature was relatively large in the spring and fall, hot and cold acclimation processes in skeletal muscle may not be fully activated in these seasons, resulting in a fluctuation in the environmental temperature influence on EE and blunting the contribution of anthropometric factors. Thus, anthropometric-based calculation of REE measured in the spring and fall should be interpreted with caution.

In concordance with the increase of REE in lower-temperature seasons, plasma T3 and NE concentrations were the highest in the Winter group and lowest in the Summer group. Thyroid hormones are known to increase the metabolic rate, and thus energy expenditure and heat production [29]. Numerous studies have revealed that thyroid hormones, especially T3, are strongly correlated with REE [30,31]. The metabolic modulating process of thyroid hormones is affected by a synergic effect of catecholamines, especially NE [29]. Thus, the increment of T3 and NE could be considered an adaptation to cold weather that consequently induces an increment of REE.

Table 2
Prevalence of metabolic status stratified by season in each gender.

	Summer	Spring	Fall	Winter	*p*
Men					
Hypermetabolism, n (%)	0 (0.0)	4 (2.7)	9 (9.9)	5 (6.2)	
Hypometabolism, n (%)	49 (73.1)	65 (44.5)	43 (47.3)	14 (17.3)	<0.001
Normometabolism, n (%)	18 (26.9)	77 (52.7)	39 (42.9)	62 (76.5)	
Women					
Hypermetabolism, n (%)	0 (0.0)	4 (2.2)	7 (5.4)	4 (4.5)	
Hypometabolism, n (%)	50 (61.7)	76 (41.3)	53 (41.1)	23 (26.1)	<0.001
Normometabolism, n (%)	31 (38.3)	104 (56.5)	69 (53.5)	61 (69.3)	

Data are presented as a number (%). *p* value was calculated by the chi square test.

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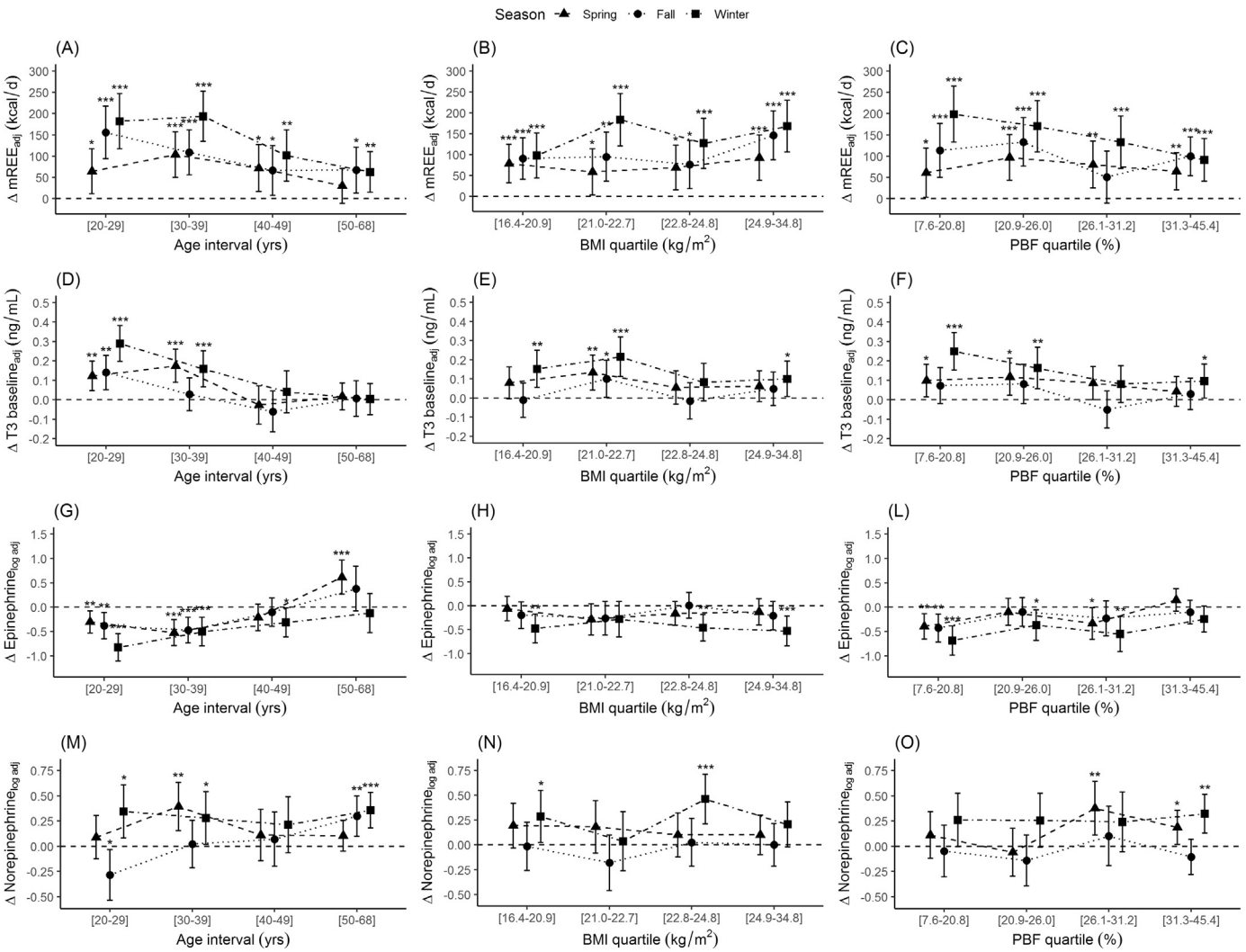

Fig. 2. Differences in measured REE, T3, epinephrine$_{log}$, and norepinephrine$_{log}$ after adjusting for age, gender, lean body mass, and percent body fat by age intervals and BMI and PBF quartiles. ANCOVA was performed using the Summer group as the reference. Significance level: *, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$. Data are shown as the mean difference and 95% confidence interval of the adjusted values. ■Solid square, ●solid circle, and ▲solid triangle represent Winter, Fall, and Spring groups, respectively.

Recently, a large number of studies have reported on the roles of thyroid hormones, especially T3, and NE on cold-induced NST related to BAT in humans. In cold exposure, conversion to T3 from T4 is promoted, and T3 in BAT cells initiates thermogenesis via an uncoupling protein process and then increases REE [12,28]. Several studies have reported a subtle increase in thyroid hormones in the winter relative to the summer [13,32,33], but others have found no difference [16]. The heterogeneity of sample populations in terms

Table 3
R-squared values of predictive models for REE using anthropometric indices and seasonal factor by the bootstrapping method.

	Whole	Spring	Summer	Fall	Winter
Model 1	0.462 (0.417–0.504)	0.436 (0.359–0.510)	0.554 (0.429–0.628)	0.443 (0.358–0.518)	0.559 (0.462–0.648)
Model 2	0.053 (0.031–0.081)	0.050 (0.016–0.098)	0.085 (0.028–0.185)	0.045 (0.007–0.110)	0.079 (0.018–0.172)
Model 3	0.643 (0.593–0.680)	0.600 (0.525–0.664)	0.772 (0.690–0.822)	0.643 (0.570–0.704)	0.753 (0.682–0.809)
Model 4	0.107 (0.071–0.150)	0.088 (0.041–0.144)	0.136 (0.052–0.240)	0.047 (0.005–0.123)	0.256 (0.150–0.358)
Model 5	0.666 (0.619–0.700)	0.634 (0.557–0.694)	0.794 (0.715–0.843)	0.679 (0.601–0.737)	0.786 (0.715–0.835)
Model 6	0.033 (0.014–0.056)				
Model 7	0.700 (0.655–0.730)	–	–	–	–

Data are presented as R squared values. The 95% confidence interval was estimated by the bootstrapping method.
Model 1: REE ~ Sex.
Model 2: REE ~ Age.
Model 3: REE ~ LBM.
Model 4: REE ~ PBF.
Model 5: REE ~ Sex + Age + LBM + PBF.
Model 6: REE ~ Season.
Model 7: REE ~ Sex + Age + LBM + PBF + Season.

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Table 4
R-squared values of predictive models for REE using anthropometric indices and seasonal factor stratified by age intervals and BMI and PBF quartiles.

	Interval 1	Interval 2	Interval 3	Interval 4
Age interval				
Model 5	0.627 (0.536–0.683)	0.668 (0.594–0.72)	0.645 (0.563–0.702)	0.724 (0.612–0.788)
Model 7	0.685 (0.586–0.733)	0.718 (0.635–0.763)	0.661 (0.575–0.716)	0.742 (0.624–0.798)
BMI quartile				
Model 5	0.517 (0.396–0.595)	0.572 (0.449–0.647)	0.617 (0.519–0.688)	0.618 (0.529–0.684)
Model 7	0.554 (0.432–0.63)	0.64 (0.541–0.702)	0.647 (0.55–0.708)	0.673 (0.591–0.728)
PBF quartile				
Model 5	0.519 (0.387–0.6)	0.669 (0.572–0.729)	0.659 (0.566–0.724)	0.664 (0.524–0.759)
Model 7	0.597 (0.487–0.664)	0.716 (0.635–0.767)	0.688 (0.57–0.748)	0.695 (0.57–0.781)

Data are presented as the R squared value. The 95% confidence interval was estimated by the bootstrapping method.
Model 5: REE ~ Sex + Age + LBM + PBF.
Model 7: REE ~ Sex + Age + LBM + PBF + Season.

of age and body composition in these studies may have caused such a discrepancy. NE is the most thermogenesis-related catecholamine in the cold adaptive response via the SNS [12,28]. The increase of cold-induced NST is associated with the elevation of NE [34,35]. Interestingly, we found a reduction of epinephrine concentration in the low-temperature seasonal groups. Although epinephrine is a catecholamine, the role of this hormone in thermogenesis to retain temperature homeostasis is limited [28]. In contrast, epinephrine is more related to thermolysis by promoting the cholinergic sweat response via both α- and β-adrenergic receptors, which are associated with eccrine sweat glands [36,37]. The elevation of epinephrine in the summer, therefore, could be explainable.

An interaction between age and seasonal changes of REE was observed in a recent study in which the difference between REE measured in the winter and summer occurred in the young population but not the elderly [14]. Consistent with these results, we found a nearly three-fold reduction in the magnitude of the winter-summer difference in the adjusted REE from the young (aged 20–29 years) to older (aged 50–69 years) age groups. The same age effect on seasonal changes in T3, but not NE, has been observed. These results suggest that aging weakens cold adaptation capacity by degrading the mitochondria uncoupling function in skeletal muscle rather than by mediating SNS functions. Evidence has shown that the prevalence of cold-induced activated BAT was 9% and 53% in elderly and young adults, respectively [38]. On the contrary, the magnitude of the winter-summer difference in the adjusted log-transformed epinephrine increased by age. This finding raises the possibility that aging may degrade hot acclimation capacity by mediating SNS responses. Our discrepancy in seasonal changes in REE and its relevance across age (between young and older individuals) may partially explain the contradictory results [13–16,19]. Age may affect body composition status.

Because the accuracy of calculation of REE is associated with BMI and fat content [6–8], we examined whether there is an interaction between the seasonal effect on REE and these confounding factors. The magnitude of the winter-summer difference in REE and T3 and the additional contribution to the anthropometric-based calculation of REE decreased from the lowest to highest PBF quartiles, but not for the BMI quartiles. In the current study, the older group had more fat, less LBM, and higher BMI than younger individuals (Supplementary S5). Thus, the PBF effect in this work may be interpreted partly by the interaction with the effect of age. BMI is not a sensitive tool to distinguish those with higher fat mass from those with higher LBM, whereas PBF is recommended as a better predictor of obesity and its related morbidity, including thermoregulation disorder. Thus, the PBF effect on seasonal changes in REE and its relevance seems to be more practical than that of the BMI effect. In the current study, the interaction term between seasonal factor and anthropometric indices was significant for age and PBF but not BMI.

The findings of this study should be considered in the context of its strengths and limitations. To our knowledge, this is the first study that employed a large sample size and examined the effects of age, BMI, and PBF in a wide range of anthropometric characteristics. Because the reference RQ range is a crucial criterion for a valid REE measurement, those with an RQ higher than 1.3 or less than 0.67 were excluded. Numerous studies in this field have not reported the selection criterion for RQ [13–16,19]. Furthermore, to eliminate the bias of disease state, several exclusion criteria for metabolic-related and thyroid functional disorders were employed. However, this cross-sectional study was not able to confirm the causal relationship between temperature changes and metabolic acclimation. Because REE measurements were not performed for each subject across seasons, the seasonal intra-individual variability of REE was not examined. The current study employed an out-patient protocol in which the participants spent the night before the measurement at home. Consequently, some pre-measurement conditions such as fasting state, physical activity, and overnight ambient temperature were not supervised strictly [39]. Several confounding factors were not controlled, such as physical exercise, energy intake, and mental stress. These findings were also based on a Korean population and therefore should not be extended to other populations.

In summary, we found that substantial seasonal changes in REE and REE-related biomarkers, such as T3, epinephrine, and NE, as well as the magnitudes of these changes, are dependent on age and PBF. The data also suggest that aging mediates cold acclimation via thyroid hormone function rather than the SNS response. Because there are seasonal alterations in the contribution of anthropometric-based predictors to the REE predictive models, the seasonal factor should be taken into account during model development.

Author contributions

Conceived and designed the experiments: CHL. Performed the experiments: DDP, JHL, KHH, YJJ, SJK, & CHL. Analyzed the data: DDP & CHL. Wrote the paper: DPP & CHL. All authors reviewed the final manuscript.

Conflict of interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2019.05.021.

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