Body fatness influences the associations between body composition and energy expenditure with energy intake in healthy women

Running title: Body fat moderates expenditure-intake associations

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What is already known about this subject?

- Fat-free mass, resting metabolic rate and total daily energy expenditure have been shown to be positively associated with daily energy intake.

- Equivocal findings have been reported regarding the association between fat mass and daily energy intake.

- Some evidence suggest that these relationships may be influenced by the levels of body fatness.

What are the new findings in your manuscript?

- The associations between resting metabolic rate and total daily energy expenditure with energy intake are moderated by body fat percentage, with the associations weakening as body fatness increases.

- The association between fat mass and energy intake may be non-linear, with fat mass negatively associated with energy intake in lean individuals but positively associated in those with overweight and obesity.

How might your results change the direction of research or the focus of clinical practice?

- Future studies should examine the physiological and/or psychological mechanisms through which body fatness alters the associations between body composition and energy expenditure with daily energy intake to help better explain energy balance dysregulation with obesity.

Abstract

Objective: To investigate the influence of body fatness on the associations between body composition and energy expenditure (EE) with energy intake (EI).

Methods: Data from 93 women (BMI=25.5±4.2kg/m^2) recruited for two studies (study 1, n=48, BMI=25.0-34.9kg/m^2; study 2, n=45, BMI=18.5-24.9kg/m^2) were examined. Body composition, resting metabolic rate (RMR) and test meal EI were assessed during a laboratory probe day. Physical activity, total daily EE (TDEE) and self-reported free-living 24-hour EI were collected during 7 days.

Results: In the whole sample, FFM (r=0.45; p<0.001), RMR (r=0.41; p<0.001), TDEE (r=0.39; p<0.001) but not FM (r=0.17; p=0.11) were positively associated with free-living 24-hour EI. Body fat percentage moderated the associations between RMR (β=-1.88; p=0.02) and TDEE (β=-1.91; p=0.03) with mean free-living 24-hour EI. FM was negatively associated with test meal EI only in the leaner group (r=-0.43; p=0.004), and a weak non-linear association was observed in the whole sample (r^2=0.092; p=0.04).

Conclusions: Body fat percentage appears to moderate the association between EE and daily EI. Furthermore, the negative association between FM and test meal EI observed in leaner individuals was absent in those with higher body fatness. Therefore, higher levels of body fatness may weaken the coupling between EE and EI.

Introduction

Understanding energy balance and the factors that lead to its dysregulation is essential to comprehend the aetiology of obesity. Recent work has highlighted body composition and energy expenditure (EE) as potential tonic drivers of day-to-day energy intake [EI; (1-3)], with associations between fat-free mass (FFM), resting metabolic rate (RMR) and EI thought to reflect the energetic demand created by metabolically active tissues (4, 5).

RMR has also been reported to be associated with the hunger sensations (6). Earlier work by Cugini et al. observed a positive association between FFM and hunger, and a negative association between fat mass (FM) and hunger in healthy individuals (7), but not in those with obesity (8). The authors postulated that this may reflect a disruption in the mechanisms that exert tonic control over daily hunger. Interestingly, Grannell et al. reported a positive association between FFM and EI at an *ad libitum* meal in 43 individuals with obesity, but the strength of this association was weaker at higher BMIs (9). Furthermore, Piaggi et al. observed a positive association between 'awake and fed thermogenesis' and total daily EI in individuals with a BMI ≤29kg/m^2 but not in those with a BMI >29kg/m^2 (10). Regarding the associations between FM and EI, equivocal findings have been reported. Negative associations between FM and EI have been observed in lean individuals (11), but studies in those with overweight/obesity often report no association between FM and EI (2, 3, 12, 13). Overall, these studies suggest that the association between body composition, EE and EI may be weaker at higher body fatness, but the potential mechanisms remain unclear and studies have yet to directly compare these associations between lean individuals and those with overweight/obesity.

Therefore, this study aimed to examine: 1) the moderating influence of body fat percentage on the associations between EE with EI, and 2) the strength and direction of the association between FM and EI across a range of body fatness.

Subjects & methods

Subjects

A total of 93 healthy women (age=35±10y; BMI=25.5±4.2kg/m^2) were included in the present analyses, with data collated from two separate studies that employed identical experimental procedures in individuals with overweight/obesity (Study 1; BMI=25.0-34.9kg/m^2) and lean (Study 2; BMI=18.5-24.9kg/m^2). Participants' descriptive characteristics can be observed in table 1 (and supplementary material table 1). The studies ran from February-September 2018 (Study 1) and from February-October 2019 (Study 2). For Study 1, participants with overweight/obesity were recruited to take part in a study examining 'the effects of a personalised weight loss meal plan on body composition and metabolism' (NCT03447600). Data reported in the present study represent baseline parameters collected before experimental diet allocation, and details of the dietary intervention are provided elsewhere (14). Study 2 was designed to provide a lean baseline comparison group for Study 1, to investigate how the influence of body composition and EE on EI and appetite differed according to body fatness.

Exclusion criteria included health problems that could affect study outcomes; history of eating disorders; medication, supplements or treatment known to affect appetite/weight; pregnancy or breastfeeding; food allergies/intolerances; smokers or recently ceased smoking (<6 months); significant weight change in the previous 6 months (±4kg); exercise >3 days per week or significant change in physical activity patterns in the past 6 months; work in appetite/feeding related areas; or shift workers. Participants were instructed not to change their physical activity and dietary habits for the duration of the study. Written informed consent was provided by all participants and the studies received approval from the School of Psychology Research Ethics Committee at the University of Leeds.

TABLE 1

Study design

In this cross-sectional study, participants completed a free-living week of measurements where body weight was measured fasted and nude each morning with a scale provided (Salter scale model 9206, UK). A digital food diary was also completed at the end of each of the 7 days and a physical activity monitor was worn continuously to assess minutes of physical activity and estimate total daily EE (TDEE). Upon completion of the measures week, participants attended the laboratory for a measures day which included assessments of body composition, RMR, objectively-measured EI and provision of a questionnaire to examine eating behaviour traits to complete at home in the evening.

Procedures

Prior to attending the laboratory sessions, participants refrained from vigorous physical activity and alcohol for 24 hours, caffeine for 12 hours, and fasted for 10-12 hours.

Resting metabolic rate

RMR was measured with an indirect calorimeter fitted with a ventilated hood (GEM, Nutren Technology Ltd). Participants were asked to remain in a supine position for 40 minutes without moving, talking or falling asleep. Before each measurement, an individual calibration process was performed. RMR was calculated using the 5-minute steady state method (15), and data was entered into the Weir equation (16).

Body Composition

Body composition was measured whilst participants were wearing tight fitting clothing and a swimming cap. FM and FFM were recorded to the nearest 0.01kg using air-displacement plethysmography (BodPod, Life Measurement, Inc., Concord, USA). Manufacturer's instructions were followed and the Siri equation (17) was used to estimate body fat percentage. FM index ($FMI=FM/height^2$) and FFM index ($FFMI=FFM/height^2$) were also calculated.

Ad libitum Test Meal Energy Intake

An *ad libitum* test meal was served 3 hours after a standardised fixed breakfast (adjusted to 25% of measured RMR; 65% carbohydrate, 15% protein, 20% fat) and comprised of risotto (Uncle Ben's Tomato & Herb; 6.32kJ/g), yoghurt (Yeo Valley Strawberry and MyProtein Maltodextrin; 6.19kJ/g) served in excess of expected consumption (70% carbohydrate, 9% protein and 21% fat) and 300g of water. For this meal, participants were instructed to eat as much or as little as they wanted until they felt comfortably full and that more food was available if needed. Between breakfast and lunch, participants could leave the laboratory but were asked not to exercise, eat or drink, except for water provided. Food items were weighed before and after consumption and macronutrient intake was calculated from the manufacturers' food labels. Test meal EI was subsequently calculated using metabolizable energy equivalents for protein, fat and carbohydrate of 16.7, 37.7 and 15.7kJ/g, respectively.

Free-Living 24-Hour Energy Intake

Myfood24 (www.myfood24.org; Version 1.0, University of Leeds, UK) is a validated online self-administered 24-hour dietary record tool (18). After a familiarisation session, participants were asked to record all food items and drinks consumed over 7 days, noting with as many details as possible when foods eaten were not in the system. Investigators manually entered the nutritional information of those foods from nutritional information provided on food packaging or from the manufacturer's website. Nutrient and energy content of foods were calculated based on the reference values of McCance and Widdowson's 6th Edition Composition of Foods UK Nutritional Dataset (19). To estimate 24-hour EI, a 7-day average was calculated and atypical days (self-reported by the participants on the website, e.g., illness) were excluded from the analyses. The EI:RMR ratio was calculated to compare the plausibility of reporting between BMI categories (20). Energy imbalance was estimated multiplying the change in body weight during the 7 days by the energy coefficient 31kJ/g (21). Mean daily EI was calculated (energy imbalance + TDEE), and this was compared to self-reported EI to examine the plausibility of reporting.

Physical Activity and Total Daily Energy Expenditure

Participants wore a physical activity monitor (SenseWear Armband; BodyMedia, Inc., Pittsburgh, USA) to measure minutes of physical activity, sedentary behaviour, and estimate TDEE over 7 days (concurrent with the 7-day food diary). TDEE and minutes spend in sedentary (<1.5METs), light (1.5-2.0METs), moderate (3.0-5.9METs) and vigorous (≥6.0METs) activities were calculated using proprietary algorithms presented in the device's accompanying software (version 8.0 professional). Participants were instructed to wear the monitor halfway between their elbow and shoulder for at least 23 hours per day, only removing during activities that involved contact with water (e.g., shower and swimming). Compliance with utilising the monitor was defined as having a minimum of 22 hours of verifiable time per day for at least 5 days (including one weekend day).

Eating Behaviour Traits

The Three-Factor Eating Questionnaire (22) is a validated 51-item scale that assesses three dimensions or eating behaviour: dietary restraint, disinhibition, and susceptibility to hunger. Responses are scored for each of the factors so that a higher score reflects a greater level of eating disturbances.

Statistical Analyses

Data throughout the text are presented as mean ± standard deviation (SD). Data were analysed using SPSS (version 25, IBM, USA). Independent samples t-tests were conducted to analyse differences between participants that were lean (study 2 – BMI=18.5-24.9kg/m^2) and with overweight/obesity (study 1 – BMI=25.0-34.9kg/m^2). Pearson's correlations were used to assess the associations between body composition, RMR and TDEE with test meal and mean 24-hour EI. Fisher Z-transformations were conducted to investigate the differences between correlations in individuals that were lean and those with overweight/obesity. Multiple linear regressions were used to examine the independent effects of body composition (FM and FFM), RMR and TDEE on test meal and mean 24-hour EI. These analyses were also repeated

using FMI and FFMI to account for differences in height (supplementary materials, tables 2-4). To test for non-linear association between FM and test meal EI, the quadratic term FM^2 was included alongside FFM and FM as predictor variables. The non-linear association was also tested using body fat percentage and FMI (supplementary material, table 5), as FM is an unstandardized measure that is influenced by body weight and height.

To examine whether body fat percentage influenced the association between RMR and TDEE with mean 24-hour EI, moderation analyses were conducted using PROCESS macro for SPSS (version 3.1) (23). Body fat percentage was used as the moderator as it has been proposed to be an important indicative of obesity-related risk factors (24). However, as body fat percentage has limitations (e.g., not accounting for height or total tissue mass), analyses were also repeated with BMI, FM and FMI as moderators (supplementary material, table 6). Eating behaviour traits and physical activity were added as covariates in the non-linear regression model and moderation analyses if they were correlated to FM and body fat percentage, respectively. These analyses were also conducted adjusting for 'study'. However, no differences were observed, and 'study' was not a significant predictor in the models.

The study was powered to examine whether the associations between body composition (FM and FFM) and EE with EI were moderated by body fat percentage (primary outcome). Power calculations (G*Power v3.1) estimated that a sample size of 77 would be required to conduct a multiple regression with 3 independent variables, a medium effect size (f^2=0.15) with α=0.05 and 1-β=0.8. Statistical significance was defined as p<0.05.

Results

As expected, FM, FMI, FFM, FFMI and body fat percentage were higher in participants with overweight/obesity (all p<0.001). FFM was a significant predictor of RMR in all BMI groups (p<0.001). RMR was not different between groups (p=0.35) but TDEE was higher in those with overweight/obesity (p<0.001). Participants with overweight/obesity had greater amounts of sedentary behaviour, and lower moderate-to-vigorous and total physical activity (all

p<0.001; table 2). The number of completed food diary days included to examine free-living 24-hour EI was 6.99±0.10 days. The EI:RMR ratio was not different between BMI categories (p=0.86). Additionally, self-reported EI was not significantly different from estimated EI in the whole sample (self-reported=7658±1630kJ/day vs estimated=8184±3381kJ/day; p=0.18) or when examined by BMI categories (lean: self-reported=7570±1580kJ/day vs estimated=8072±3043kJ/day, p=0.29; overweight/obesity: self-reported=7741±1685kJ/day vs estimated=8297±3708kJ/day, p=0.39), suggesting that plausibility of reporting was similar between groups.

TABLE 2

Associations Between Body Composition, Energy Expenditure and Energy Intake

FFM (r=0.45; p<0.001), RMR (r=0.41; p<0.001) and TDEE (r=0.39; p<0.001), but not FM (r=0.17; p=0.11), were positively associated with mean 24-hour EI (figure 1). Similar findings were observed using FFMI and FMI (supplementary material, figure 1). No associations were observed between body composition and EE with test meal EI in the whole sample (all p≥0.13).

FIGURE 1

To examine the independent effects of body composition and EE on mean 24-hour EI, three multiple linear regressions were conducted in the whole sample. In model 1, FM and FFM accounted for 19% of the variance in mean 24-hour EI [$F_{(2, 90)}$=11.5, r^2=0.19, p<0.001], with FFM the only predictor (β=0.47; p<0.001). Adding RMR in model 2 [$F_{(3, 89)}$=8.2, r^2=0.19, p<0.001], or TDEE in model 3 [$F_{(3, 88)}$=7.9, r^2=0.18, p<0.001] did not increase the variance in mean 24-hour EI explained by the model. These analyses were replicated using FMI and FFMI (supplementary material, table 2). When models 1-3 were replicated with test meal EI as the dependent variable, none of the models explained the between-subject variance in test meal EI (all models r^2=0.006-0.04; p=0.42-0.78).

Differences Between Lean Individuals and Those with Overweight/Obesity

The associations between FFM, RMR and TDEE with mean 24-hour EI can be seen in figure 2. While these were stronger in leaner participants, Fisher Z-transformations indicated that the differences in r values between BMI categories did not reach significance (FFM: Z=0.73, p=0.23; RMR: Z=1.27, p=0.10; TDEE: Z=1.54, p=0.06). No associations were observed between FM and mean 24-hour EI in either group (figure 2). Two regression models to predict mean 24-hour EI were conducted for each BMI group (Model 1 – FM and FFM; Model 2 – FM, FFM and RMR). FFM was a predictor of mean 24-hour EI in both models and both groups (all p≤0.04), but RMR was only a predictor in the leaner group (β=0.35; p=0.04; overweight/obesity, p=0.53), suggesting that a moderating effect of body fatness could be present. FM was not a predictor of mean 24-hour EI in any models (all p>0.32). Similar findings were observed with FMI and FFMI (supplementary material, table 4).

FIGURE 2

A negative association between FM and test meal EI was observed in leaner participants (r=-0.43; p=0.004), but not in those with overweight/obesity (r=0.23; p=0.11), and these r values were significantly different (Z=-3.24; p=0.001). No other associations between body composition and EE with test meal EI existed in either group (all p≥0.11). Those with overweight/obesity were also analysed separately (BMI=25.0-29.9kg/m^2 and BMI=30.0-34.9kg/m^2). There were no associations between FM and test meal EI in the group that had overweight, but a trend for a positive association emerged in those with obesity (r=0.41, p=0.12; figure 3-A). Similar findings were observed with FMI (supplementary material, figure 2).

As the direction of the association between FM and test meal EI changed with increased body fatness (figure 3-A) a non-linear (quadratic) regression was tested. While FM and FFM failed to explain the variance in test meal EI [$F_{(2,89)}=0.29$, $r^2=0.006$, p=0.75], the addition of the quadratic term FM^2 (β=0.46; p<0.001) explained an additional 9% of the variance [$F_{(3, 88)}=3.0$,

r^2=0.092, p=0.04; figure 3-B]. Disinhibition (r=0.42; p<0.001), total physical activity (r=-0.55; p<0.001), sedentary time (r=0.56; p<0.001) and moderate-to-vigorous physical activity (r=-0.49; p<0.001) were correlated to FM and therefore were added as covariates in the multiple regression. Their addition did not influence the β or statistical significance of the quadratic term and were not found to predict test meal EI (all p≥0.12). This non-linear association was similar when FMI or body fat percentage were used (supplementary material, table 5).

FIGURE 3

Moderation Analyses

An interaction was found in which body fat percentage (β=-1.88; p=0.02) moderated the association between RMR and mean 24-hour EI [F(3, 89)=8.1, r^2=0.21, p<0.001]. Body fat percentage was also found to moderate (β=-1.91; p=0.03) the association between TDEE and mean 24-hour EI [F(3, 88)=6.8, r^2=0.19, p<0.001]. Participants with a lower body fat percentage (-1SD) presented stronger associations between RMR and TDEE with mean 24-hour EI and these weakened with increased body fatness (figure 4).

Disinhibition (r=0.41; p<0.001), total physical activity (r=-0.57; p<0.001), sedentary time (r=0.59; p<0.001) and moderate-to-vigorous physical activity (r=-0.49; p<0.001) were correlated with body fat percentage, and were therefore added as covariates in the moderation analyses. This moderating effect remained significant after their inclusion and none of them predicted mean 24-hour EI (all p≥0.08). The moderation effect remained unchanged when BMI, FM and FMI were used as moderators (supplementary material, table 6).

FIGURE 4

Discussion

This study investigated if body fat percentage moderated the associations between EE and EI, and how the strength and direction of the association between FM and EI differed across a range of body fatness. FFM, RMR and TDEE were positively associated with mean 24-hour

EI. Notably, body fat percentage moderated the association between RMR and TDEE with mean 24-hour EI, in which participants with a lower body fat percentage presented stronger positive associations. A non-linear association between FM and objectively-measured test meal EI was also demonstrated, with a negative association observed between FM and EI in participants that were lean but not in individuals with overweight/obesity. These data suggest that the associations between components of body composition and EE with EI are weaker in those with higher body fatness.

Associations between Fat-free Mass, Energy Expenditure and Energy Intake

In line with previous findings (3-5, 11, 13, 25, 26), FFM and RMR were positively associated with mean 24-hour EI (but not intake at the test meal). Importantly, data from the present study extend previous findings by demonstrating quantitatively that body fat percentage moderates the association between RMR and TDEE with mean 24-hour EI. This moderation effect remained significant after accounting for potential covariates such as eating behaviour traits (4) and physical activity (27), and when other markers of body fat were used as moderators (FM, FMI and BMI).

These data suggest that the strength of the association between RMR and TDEE with EI is weaker at higher body fatness, and are in agreement with previous research (7-10). These findings corroborate those of Grannell et al., that observed an interaction between FFM and BMI in which the association between FFM and EI was weaker at higher BMIs. In the present study, an interaction between FFM and body fat percentage was also observed [$F_{(3, 89)}=9.7$, $r^2=0.25$, $p<0.001$; interaction term - $\beta=-1.85$; $p=0.03$]. It has previously been suggested that under conditions of approximate energy balance the associations between FFM, RMR and EI reflect a 'mass-dependent' tonic drive to eat arising from the energy turnover of metabolically active tissues (4, 5, 28). In line with the present data, a weaker association between RMR and EI at higher body fatness might be expected given the disproportionate changes seen in FFM

and FM with weight gain. As body weight increases, FM is disproportionately increased relative to FFM (29), thus making the relationship between RMR and body weight curvilinear (30). This may lead to a non-linear relationship between RMR and EI in which RMR contributes less to the drive to eat at higher body fatness. This could in part explain the lack of significant differences in RMR between BMI groups despite the higher body weight in those with overweight/obesity. Of note, body composition was assessed in the present study using a 2-compartment model, which does not allow examination of specific components of FFM. As these tissues present different metabolic rates (31-33), future studies should examine how differences in the composition of FFM at higher levels of body fatness influence EI.

Associations Between Fat Mass and Energy Intake

No associations were observed between FM and mean 24-hour or test meal EI in the whole sample. However, after splitting the sample into lean, overweight and obese BMI categories, the association between FM and test meal EI was negative in the leaner group but positive in the group with obesity. While it is acknowledged that the number of participants in the group with obesity was small (and likely underpowered to detect a significant association), regression analysis in the whole sample using the quadratic term FM^2 indicated that the association between FM and test meal EI was non-linear. These findings suggest that the associations between FM and EI may change from negative to positive at higher body fatness. While a negative association between FM and EI has previously been reported in lean individuals (7, 26), findings in individuals with overweight/obesity often demonstrate no association (2, 3, 12, 13). These data have been used to argue that as FM is gained, the inhibitory influence of FM on EI proportionally weakens (9, 11). However, it is worth noting that under conditions of weight stability and approximate energy balance, the influence of fat mass on day-to-day food intake actually appears relatively weak (as evidenced by the ease at which people gain weight with energy surfeit). Reductions in fat mass may have greater biological relevance for the control of appetite during weight loss.

A weaker negative association between FM and EI at higher body fatness is in line with the notion of leptin and insulin resistance (34, 35), which may alter central and peripheral sensitivity to appetite-related feedback signals (36-38). Altered fasting and postprandial appetite-related peptide secretion has also been found in individuals with obesity (36). Furthermore, while the contribution of FM to RMR is smaller than of FFM (39), it would be expected that its absolute contribution to RMR will become proportionally larger as FM increases with weight gain. Therefore, it could be hypothesised that differences in the strength (i.e., weaker) and direction (i.e., more positive) of the association between FM and EI at higher body fatness may reflect the increased contribution of FM to total body weight and RMR alongside a blunting of its inhibitory influence on EI. However, the cross-sectional nature of the present and previous studies means that this hypothesis needs to be examined in studies where FM, FFM and EE are systemically manipulated. Indeed, the associations between components of body composition and EE may differ during weight loss (40-42). Further research is also needed to rule out potential confounders of FM and EI relationships along the spectrum of BMI, such as body image concerns and self-regulation of EI which co-vary with adiposity and may be more evident in lean subjects. It has also been shown that the negative association between FM and EI may be stronger in more active individuals (43). The absence of an influence of physical activity on the current findings could be due to limiting exercise to ≤3 times per week. Physical activity or cognitive restraint did not influence the reported associations in the present study, but given the equivocal findings in studies examining the associations between FM and EI, these results need to be replicated and the potential physiological, behavioural and psychological mechanisms underlying any differences between lean individuals and those with overweight/obesity examined.

Limitations

TDEE was assessed using accelerometry rather than doubly-labelled water, but the device used here (SenseWear Armband) has been shown to provide valid estimates of TDEE (44) and minimum wearable time was set at 22 hours per day to improve estimates. Free-living 24-

hour EI was assessed using an online self-report tool, which is susceptible to various forms of misreporting. Greater underreporting has been observed in individuals with overweight/obesity (45), but in this study the EI:RMR ratio and difference between self-reported and calculated EI was similar between BMI categories, suggesting that the extent of misreporting did not differ between groups. The association between FFM and EI has previously been shown to be weaker with self-reported data in comparison to objectively measured EI, but the underlying association remained evident (46). The strength of the association between FFM or RMR and EI in the present data (r=0.45 and r=0.41, respectively) were similar to the values observed in studies using laboratory based measurements [r=0.22–0.69 (2, 6, 26)]. It is relevant to mention that the current analyses were conducted in women. Unfortunately, there are currently no published data that specifically examine how sex influences the strength of these associations, and given the known sex differences regarding body composition, this should be addressed in future research. It is important to acknowledge that these associations represent statistical rather than biological pathways. Although these analyses may oversimplify the underlying biological mechanisms influencing energy balance, our data demonstrate that the inter-relationships between body composition, EE and EI are likely to be non-linear. These data are also cross-sectional in nature, and future studies should assess how the strength and direction of the associations between components of body composition, EE and daily EI change with controlled weight loss or gain.

Conclusion

This study demonstrates that body fat percentage moderates the associations between RMR and TDEE with daily EI. Furthermore, a negative association between FM and test meal EI was observed in lean participants but not in those with overweight/obesity. These data suggest that the influence of body composition and EE on EI is weaker in those with higher body fatness. Therefore, greater FM may be associated with energy balance dysregulation and a weaker coupling between EE and EI.

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