



The effect of severe obesity on three-dimensional ground reaction force signals during walking

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ABSTRACT

Background: The gait pattern of adults with class I obesity [$30 \leq$ body mass index $< 35 \text{ kg/m}^2$] was characterized by altered three-dimensional ground reaction force signals compared to lean adults ($18.5 \leq$ body mass index $< 25 \text{ kg/m}^2$). However, results might not be generalizable to adults with severe obesity (class II and III; body mass index $\geq 35 \text{ kg/m}^2$). Hence, the purpose of the present study was to investigate the differences in relative ground reaction force signals, i.e., normalized by body weight, between adults with severe obesity and lean adults using functional principal component analysis.

Methods: Thirteen lean and eighteen sedentary adults with severe obesity performed a 5-min walking trial (1.11 m/s) on an instrumented treadmill. The first five functional principal components of the relative force signals (mediolateral, anterior-posterior, and vertical directions) were obtained using functional principal component analysis. Functional principal component scores were compared between groups using an analysis of covariance with age as covariable.

Findings: Functional principal component analysis reported a statistically significant group effect for first functional principal component score for mediolateral ($P = 0.004$), and second and fifth functional principal component scores for anterior-posterior ($P \leq 0.02$) force signals. Adults with severe obesity displayed a greater mediolateral force during most of the stance but similar magnitudes of the anterior-posterior and vertical forces compared to lean adults.

Interpretation: Therefore, increasing the obesity level accentuates differences in mediolateral force but promotes no specific changes in anterior-posterior force likely due to chronic loading adaptation.

1. Introduction

The prevalence of obesity increases across the world and represents a global public health issue (NCD-RisC, 2017). Obesity is defined as an excessive or abnormal fat accumulation which presents health risks related to multiple chronic conditions (World Health Organization, 2000). According to the World Health Organization, the level of obesity could be assessed using the body mass index (BMI; kg/m^2) and defined by three classes: class I ($30 \leq \text{BMI} < 35 \text{ kg/m}^2$), II ($35 \leq \text{BMI} < 40 \text{ kg/m}^2$), and III ($\text{BMI} \geq 40 \text{ kg/m}^2$) (World Health Organization, 2000). Class I obesity is also called moderate obesity while class II and III could be combined and called severe obesity (Berrington de Gonzalez et al., 2010).

The gait pattern of adults with overweight and obesity was characterized by less knee and hip flexion and extension (McMillan et al., 2010), as well as altered three-dimensional (3D) ground reaction force (GRF) signals (Browning and Kram, 2007; Kim et al., 2022) compared to lean adults ($18.5 \leq \text{BMI} < 25 \text{ kg/m}^2$). Moreover, obesity induces a greater lower limb mechanical joint loading while walking, which might increase the risk of falling (Gill and Narain, 2012) as well as the risk to develop lower limb traumatic injuries (Byrnes et al., 2005; Soliman et al., 2022) and articular cartilage diseases (Bourne et al., 2007; Coggon et al., 2001). These traumatic injuries and articular diseases could be detected using the 3D GRF signals. In fact, individuals with knee osteoarthritis showed 54% greater relative mediolateral GRF [the term *relative* refers to the fact that the force is expressed in percentage of body

Abbreviations: 3D, three-dimensional; BMI, body mass index; BW, body weight; FPC, functional principal component; FPCA, functional principal component analysis; GRF, ground reaction force.

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weight (BW)], after heel-strike compared to a control group (Mündermann et al., 2005). Hence, the altered mediolateral GRF signal of adults with obesity compared to lean adults could be a biomechanical precursor of lower limb injuries (Kim et al., 2022).

Data reduction is critical in gait analysis (Chau, 2001), and principal component analysis (PCA) can be particularly useful to reduce data dimensionality with maximally preserving data variance (Jolliffe and Cadima, 2016). Subjective selections of discrete data points may miss critical temporal information and limit the holistic understanding (Deluzio and Astephen, 2007). Thus, a multivariate analysis method, the functional PCA (FPCA), might be preferred to analyze the entire time series of GRF data. Recently, Kim et al. (2022) reported that both overweight ($25 \leq \text{BMI} < 30 \text{ kg/m}^2$)/moderate obesity and older groups showed a greater relative braking force after heel-strike and a greater relative propulsive force during pre-swing compared to lean adults and younger group, respectively, using FPCA. In addition, older individuals with overweight displayed a greater relative mediolateral force during mid-stance and young adults with overweight showed a prominently larger relative mediolateral force and more dynamic patterns during pre-swing. Nonetheless, the authors acknowledged that their results might not be generalizable to individuals with higher BMI ($\geq 35 \text{ kg/m}^2$; severe obesity). In fact, it has been recently shown that level of obesity influences the energetics and mechanics of walking (Primavesi et al., 2021). Only individuals with severe obesity, and not with moderate obesity, can optimally exploit lateral movements of the center of mass to enhance the pendular mechanism during walking and thus partially mitigate the higher energy cost of walking compared with lean adults (Primavesi et al., 2021).

Hence, the purpose of the present study was to investigate the differences in 3D relative GRF signals between adults with severe obesity and lean adults using FPCA. We hypothesized that the features of the 3D relative GRF signals during walking would manifest differently between adults with severe obesity and lean adults and would be similar or even more accentuated to those reported by Kim et al. (2022), i.e., adults with severe obesity would display a greater relative mediolateral force during mid-stance and pre-swing as well as a greater relative braking force after heel-strike and a greater relative propulsive force during pre-swing compared to lean adults.

2. Methods

2.1. Participant characteristics

Thirteen healthy, nontrained, and normally active lean and eighteen sedentary (no participation in any regular exercise or $\leq 2 \text{ h}$ of physical activity per week over the past year) adults with severe obesity (class II: $N = 10$; $\text{BMI} = 37 \pm 2 \text{ kg/m}^2$ and class III: $N = 8$; $\text{BMI} = 44 \pm 3 \text{ kg/m}^2$) voluntarily participated in this study. All participants with obesity were healthy and free of musculoskeletal injuries and cardiovascular and respiratory diseases that could affect their gait pattern. Based on a medical exam, the exclusion criteria were neurological disorders, orthopedic injury, cardiovascular diseases, history of falls, and medications that provoke dizziness. Adults with severe obesity were significantly older and heavier than lean adults ($P \leq 0.006$; Table 1),

Table 1
Anthropometric characteristics of participants.

Variables	Lean adults	Adults with severe obesity	P
Sex	M = 5; F = 8	M = 4; F = 14	NA
Age (y)	30 ± 6 [25, 44]	37 ± 8 [24, 55]	0.006
Height (cm)	171 ± 9 [157, 185]	166 ± 7 [155, 187]	0.09
Mass (kg)	64 ± 8 [50, 77]	110 ± 13 [88, 127]	<0.001
BMI (kg/m^2)	22 ± 1 [19, 24]	40 ± 4 [35, 50]	NA

Values are given as mean \pm standard deviation and [min, max]. M: male, F: female, and BMI: body mass index. Significant differences ($P \leq 0.05$) are reported in bold.

whereas the height of the two groups was similar (Table 1). The number of participants per group herein is similar to those previously employed in Kim et al. (2022), i.e., 12 to 16 participants per group. The dataset for this study was extracted from our laboratory database, which was essentially composed of data from two previously published studies of our research group, for which the participants gave their agreement to the publication of the data obtained during the experiment (Fernández Menéndez et al., 2019; Fernández Menéndez et al., 2020). These studies were approved by the local ethics committee (CER-VD 136/14—CER-VD 2016–01715) and adhered to the Declaration of Helsinki of the World Medical Association. Lean adults ($18.5 \leq \text{BMI} < 25 \text{ kg/m}^2$) and individuals with severe obesity ($\text{BMI} \geq 35 \text{ kg/m}^2$) walking at 1.11 m/s were selected. This speed is similar to the preferred walking speed of such population (Malatesta et al., 2022) and corresponds to the speed evaluated in Kim et al. (2022). Participants provided written informed consent before testing.

2.2. Experimental procedure

Participants visited the laboratory once to perform (1) a 10-min treadmill familiarization session (Wall and Charteris, 1981) and (2) a 5-min level walking trial at 1.11 m/s on an instrumented single-belt treadmill (T10-FMT-MED, Arsalis, Louvain-la-Neuve, Belgium). 3D GRF signals (sampling rate: 1000 Hz) were collected during 20 consecutive steps in the last minute of the walking trial. All participants wore their habitual walking shoes (training shoes).

2.3. Data processing

Force data were filtered with a 10th-order Butterworth filter at a cut-off frequency of 20, 20, and 15 Hz for vertical, anterior-posterior, and mediolateral GRFs and normalized by BW, leading to relative forces. An algorithm was applied to these filtered 3D force data to recover the 3D force data under each foot (Bastien et al., 2019; Meurisse et al., 2016). This algorithm returns the 3D force under each foot and the corresponding stance phases, which are determined using a 0 N vertical threshold. Then, these relative force data were time-normalized to the total stance time by using 101 data points (i.e., by rescaling stance time to 0–100%), and an ensemble-averaged data set from the 20 steps was produced using python (v3.7.4, available at <http://www.python.org>).

FPCA was performed using the python package scikit-fda (retrieved from <https://fda.readthedocs.io/en/latest/index.html>) to obtain the first five functional principal components (FPCs) of the relative GRF signals in the mediolateral, anterior-posterior, and vertical directions. FPCA, which is based on PCA but uses the variability of a sample of curves (or functions) as input, was preferred over PCA because there are no instability issues when using a signal as input, i.e., when the number of points in the signal is larger than the sample size (Castro et al., 1986; Coffey et al., 2011; Dauxois et al., 1982). Moreover, FPCA, as PCA, allows interpreting the 3D relative GRF signals by generating a small number but critical features. This dimensionality-reduction method further allows the researchers to not miss critical information by subjectively selecting specific data points (i.e., at a specific time) in the 3D relative GRF signals (Deluzio and Astephen, 2007).

2.4. Statistical analysis

Descriptive statistics are reported as mean \pm standard deviation. Normality of data (participant characteristics and FPC scores) was verified using Kolmogorov-Smirnov test ($P \geq 0.31$). Student's *t*-tests were used to compare participant characteristics between groups. Age being statistically different between groups (Table 1), analysis of covariance (ANCOVA) was used with age as a covariable to compare walking gait (FPC scores) between groups. Statistical analysis was performed using Jamovi (v1.6, retrieved from <https://www.jamovi.org>) with a level of significance set at $P \leq 0.05$.

3. Results

FPCA models using five FPCs were created for the GRF signal in each direction. These models explained 89.4, 89.1, and 84.8% of the variance in the mediolateral, anterior-posterior, and vertical axis, respectively (Table 2). The first FPC score for mediolateral and second and fifth FPC scores for anterior-posterior GRF signals demonstrated a statistically significant group effect while there was no significant difference in FPC score between groups for the vertical GRF signal. Biomechanical interpretations of the corresponding FPCs were made based on the loading vectors, the reconstructed relative force signals obtained using these loading vectors for subjects with the 10% lowest and 10% highest FPC scores (which allows to obtain a reconstructed signal representative of the participants, i.e., 4 herein, with the lowest and highest scores), and the average GRF signals (Figs. 1-2).

3.1. Relative mediolateral ground reaction force

Adults with severe obesity depicted larger magnitudes of the relative mediolateral force signal during most of the stance compared to lean adults (Fig. 1A). The first mediolateral FPC (63.1% variation explained) captured the overall magnitude of the relative mediolateral force signal (Fig. 1C and D). Adults with severe obesity reported significantly higher FPC scores than lean adults ($P = 0.004$; Table 2; Fig. 1B). There was no effect of the covariable age ($P \geq 0.07$).

3.2. Relative anterior-posterior ground reaction force

Individuals with severe obesity depicted similar magnitudes of the relative anterior-posterior force signal during the braking and propulsive phases (Fig. 2A). The second anterior-posterior FPC (24.0% variation explained) captured the magnitude of the braking peak of the relative anterior-posterior force signal (Fig. 2C and D). Adults with severe obesity reported significantly lower second FPC scores than lean adults ($P = 0.02$; Table 2; Fig. 2B). The fifth anterior-posterior FPC (5.0% variation explained) captured the braking rate and the magnitude of the propulsive peak of the relative anterior-posterior force signal (Fig. 2F and G). Adults with severe obesity reported significantly higher fifth FPC scores than lean adults ($P = 0.01$; Table 2; Fig. 2E). A statistically significant effect of the covariable age was reported for the second FPC score of the anterior-posterior GRF signal, with older people depicting larger FPC scores ($P = 0.04$; Table 2).

Table 2

Functional principal component analysis and analysis of covariance (group effect and covariable age effect) results for three-dimensional relative ground reaction force.

Relative force	FPC	Variance explained (%)	Lean adults FPC score	Adults with severe obesity FPC score	Group effect P	Covariable age effect P	Biomechanical description
Mediolateral	1	63.1	-5.4 ± 4.4	3.9 ± 7.9	0.004	0.67	Overall magnitude
	2	13.5	-0.14 ± 1.5	0.10 ± 4.8	0.46	0.07	
	3	5.3	0.38 ± 2.5	-0.27 ± 2.3	0.35	0.54	
	4	4.7	-0.78 ± 1.9	0.56 ± 2.3	0.25	0.52	
	5	2.8	-0.36 ± 1.8	0.26 ± 1.6	0.37	0.91	
Anterior-posterior	1	36.9	2.9 ± 5.6	-2.1 ± 5.9	0.11	0.40	Magnitude of the braking peak
	2	24.0	1.7 ± 4.8	-1.2 ± 4.9	0.02	0.04	
	3	13.5	-0.38 ± 3.8	0.28 ± 3.8	0.94	0.31	
	4	9.7	0.03 ± 4.4	-0.02 ± 2.0	0.94	0.94	
	5	5.0	-1.1 ± 2.0	0.82 ± 2.2	0.01	0.44	
Vertical	1	29.5	-2.4 ± 4.7	1.7 ± 5.6	0.06	0.84	Braking rate and magnitude of the propulsive peak
	2	22.4	1.4 ± 5.9	-1.0 ± 3.7	0.26	0.92	
	3	16.9	-1.6 ± 2.7	1.1 ± 4.7	0.36	0.14	
	4	10.4	0.66 ± 3.6	-0.47 ± 3.0	0.18	0.26	
	5	5.6	-0.03 ± 1.4	0.02 ± 3.0	1.00	0.92	

Values are given as mean \pm standard deviation. Significant differences ($P \leq 0.05$) are reported in bold. Functional principal components (FPCs), variance explained, FPC scores for lean adults and adults with severe obesity, significant differences between these groups, and significant differences of the covariable age. A biomechanical description of the FPCs was given only for those that exhibited a statistically significant group effect on the FPC scores.

3.3. Relative vertical ground reaction force

Adults with severe obesity depicted similar or slightly smaller magnitudes of the relative vertical force signal compared to lean adults but the first peak occurred slightly later in the stance for individuals with severe obesity compared to lean adults (Fig. 3). There was no significant difference in FPC score between groups for the vertical GRF signal ($P \geq 0.06$) as well as no effect of the covariable age ($P \geq 0.14$; Table 2).

4. Discussion

The purpose of the present study was to investigate the differences in 3D relative GRF signals between adults with severe obesity ($BMI \geq 35 \text{ kg/m}^2$) and lean adults using FPCA. Adults with severe obesity displayed a greater relative mediolateral force during most of the stance compared to lean adults, supporting our hypothesis. However, there was no difference in relative braking force after heel-strike and relative propulsive force during pre-swing, partly refuting our hypothesis. In addition, adults with severe obesity showed similar vertical force signal compared to lean adults.

The first mediolateral FPC score (Table 2 and Fig. 1B-D) indicates that adults with severe obesity have greater relative mediolateral force during most of the stance compared to lean adults. Hence, increasing the level of obesity shifts upward the overall relative mediolateral force curve corroborating previous findings in adults with overweight and class I (Kim et al., 2022) and class II (Browning and Kram, 2007) obesity. Browning and Kram (2007) obtained that the increase in mediolateral force was disproportionate compared to the difference in body mass between adults with class I and II obesity and lean adults. These authors attributed this disproportion to the significantly and 30% greater step width of adults with obesity compared to lean adults during walking. This latter may represent an active strategy to increase gait dynamic balance or may simply reflect the greater girth of the thigh and lower limb in adults with obesity compared to lean individuals (Spyropoulos et al., 1991). This greater relative mediolateral force during early stance may also be due to the increased muscle force needed to control the degree of pronation. The degree of pronation has been reported to be larger and more difficult to control in adults with obesity than in lean individuals (Browning and Kram, 2007; Messier et al., 1994). Moreover, only adults with severe obesity can optimally exploit these greater lateral displacements to enhance the pendular energy recovery mechanisms to partially mitigate the increase in energy cost of walking with

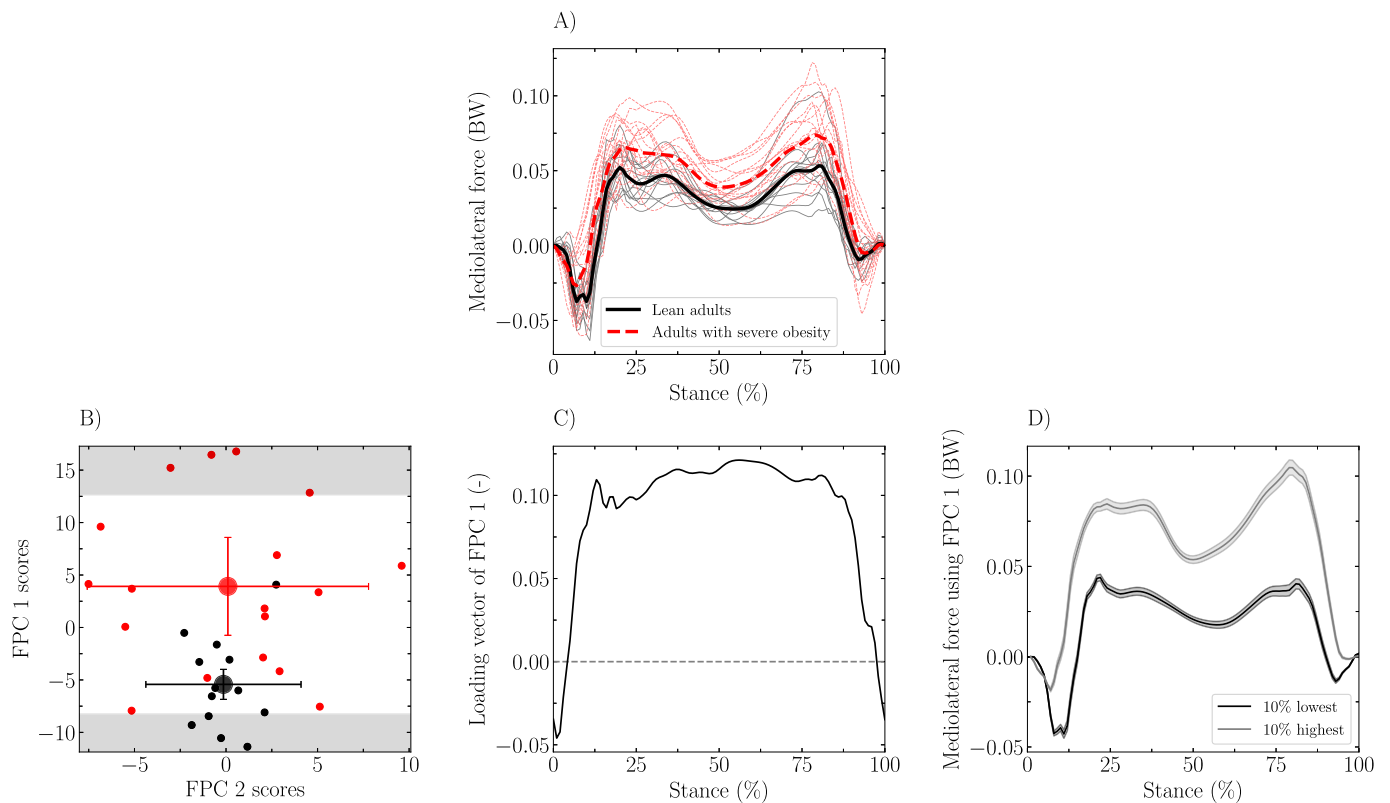


Fig. 1. (A) Relative mediolateral ground reaction force signal [expressed in body weight (BW)] during stance and for all participants within lean adults (dashed red line) and adults with severe obesity (solid black line) and the overall average curve (thicker dashed red and solid black lines) for both groups, (B) first as a function of second functional principal component (FPC) scores for lean adults and adults with severe obesity, (C) loading vector of the first FPC during stance, and (D) relative mediolateral force reconstructed using the first FPC in BW for subjects with the 10% lowest and 10% highest FPC scores during stance [these subjects are those within the lower and upper gray shaded areas in (B)]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

respect to lean adults (Primavesi et al., 2021). However, this greater relative mediolateral force during stance with obesity may result in deleterious overloads on the articular cartilage (Farahpour et al., 2016; Kim et al., 2022; Kim and Zhang, 2017; Smith et al., 1995). For instance, individuals with knee osteoarthritis showed alterations of their mediolateral GRF signal during walking (Costello et al., 2019) and up to 54% greater relative mediolateral GRF after heel-strike (Mündermann et al., 2005) compared to a control group. Hence, the alteration of the relative mediolateral GRF signal in adults with severe obesity compared to lean adults could be a biomechanical precursor of lower limb injuries in this population (Kim et al., 2022). This is relevant because, each year, musculoskeletal injuries account for ~8% of the dropouts from exercise training programs in habitual walkers with overweight or obesity (Hootman et al., 2002).

The second and fifth anterior-posterior FPC scores (Table 2 and Fig. 2B-G) indicate that adults with severe obesity have a lower magnitude of the braking peak of the relative anterior-posterior force signal compared to lean adults and higher braking rate and magnitude of the propulsive peak of the relative anterior-posterior force signal compared to lean adults, respectively. However, overall similar magnitudes of the relative anterior-posterior force signal during the braking and propulsive phases were reported (Fig. 2A), suggesting that the first five FPCs might compensate each other around the braking and propulsive peaks. These results are inconsistent with a previous study reporting higher anterior-posterior force during the braking phase in adults with obesity compared to lean adults (Silva et al., 2018) for attenuating the center of mass forward progression during early stance. In addition, these results contradict previous findings which reported greater anterior-posterior braking and propulsive peaks in adults with a lower level of obesity compared to lean adults walking at self-selected

walking speed (Kim et al., 2022). Moreover, this previous study also found that adults with obesity showed a delay in the pre-swing peak compared to lean adults (Kim et al., 2022), a feature which was not reported herein. Therefore, taken together our results highlight that severe obesity does not induce a specific change in the relative anterior-posterior force during walking compared to a lower level of obesity (Kim et al., 2022).

Adults with severe obesity depicted similar and slightly smaller magnitudes of the relative vertical force signal compared to lean adults (Fig. 3) but the first peak (i.e., loading response) occurred slightly later in the stance for individuals with severe obesity compared to lean adults. These findings are in line with previous results reporting similar relative peaks of vertical force during stance in individuals with class I and II obesity (i.e., higher level of obesity) compared to lean adults walking at a fixed speed similar to that used in the present study (1.0 vs 1.1 m/s) (Pamukoff et al., 2016; Vakula et al., 2019). However, the present results contradict previous findings which reported larger fluctuations of the vertical force and a phase shift in the pre-swing phase (the peak occurs later) for adults with overweight and class I obesity compared to lean adults (Kim et al., 2022). Nonetheless, the absolute vertical force increases in almost direct proportion with BW during walking (Brown and Kram, 2007) and reflects the higher loads placed upon the joints of the lower limbs during walking in adults with severe obesity (Vakula et al., 2019). This higher load may induce a delayed first peak (in percentage of stance) during loading response indicating that adults with severe obesity might need more time for weight acceptance, as slightly observed in Fig. 3.

As adults with severe obesity were significantly older than lean adults, age was used as a covariable in the present analyses. A significant positive effect of the covariable age was reported only for the second

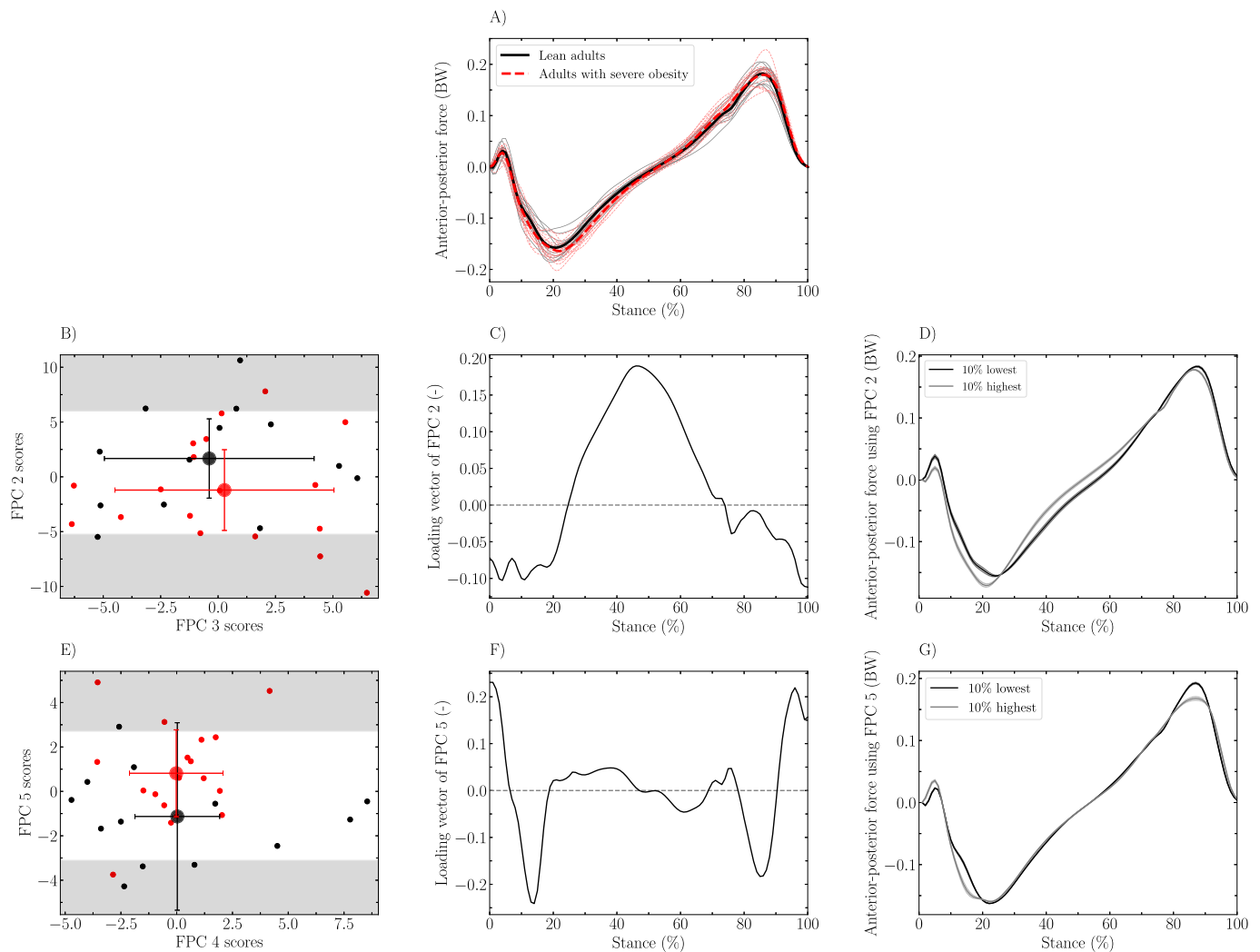


Fig. 2. (A) Relative anterior-posterior ground reaction force signal [expressed in body weight (BW)] during stance and for all participants within lean adults (dashed red line) and adults with severe obesity (solid black line) and the overall average curve (thicker dashed red and solid black lines) for both groups, (B) second as a function of third functional principal component (FPC) scores for lean adults and adults with severe obesity, (C) loading vector of the second FPC during stance, (D) relative anterior-posterior force reconstructed using the second FPC in BW for subjects with the 10% lowest and 10% highest FPC scores during stance [these subjects are those within the lower and upper gray shaded areas in (B)], (E) fifth as a function of fourth FPC scores for lean adults and adults with severe obesity, (F) loading vector of the fifth FPC during stance, and (G) relative anterior-posterior force reconstructed using the fifth FPC in BW for subjects with the 10% lowest and 10% highest FPC scores during stance [these subjects are those within the lower and upper gray shaded areas in (E)]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

FPC score of the anterior-posterior GRF signal, with older people depicting larger FPC scores (Table 2). All participants in this study were no older than 65 years, which is considered the critical age for substantially changing energetics and mechanics of walking (Malatesta et al., 2003; Malatesta et al., 2004). Hence, the effect of age might be considered as negligible in the present study.

The following limitations of the present study need to be considered. First, adults with severe obesity could be prone to more gait fatigue than lean adults, amplifying the differences observed herein as those were investigated during the last minute of the 5-min walking trial. However, during experiments performed in previously published studies and from which these data have been extracted (Fernández Menéndez et al., 2019; Fernández Menéndez et al., 2020), the walking trials were randomized and interspersed with a 5-min recovery period. In addition, all participants reached a metabolic steady-state at the end of each walking trial attesting no apparent difference in the level of fatigue between lean adults and adults with severe obesity. Second, several studies analyzed data obtained from force platforms placed along a walkway [e.g., Pamukoff et al., 2016, Vakula et al., 2019, or Kim et al., 2022] while

others analyzed data obtained from an instrumented treadmill [e.g., Browning and Kram, 2007 or Primavesi et al., 2021]. However, a recent review reported that spatiotemporal and kinetic measures were largely comparable for motorized treadmill and overground walking (Semaan et al., 2022). Third, grouping class II and class III obesity increased statistical power and was justified because the risk of mortality increased similarly in individuals with class II and III obesity (Berrington de Gonzalez et al., 2010). However, it might also have influenced the results of the present study. Indeed, this did not allow us to examine if changes in relative anterior-posterior force with increasing levels of obesity were gradual or discontinuous, hence warranting further investigation.

5. Conclusions

In conclusion, distinct features of the 3D relative GRF signals were identified between adults with severe obesity ($\text{BMI} \geq 35 \text{ kg/m}^2$) and lean adults during the stance walking phase and using FPCA. FPC scores of adults with severe obesity were significantly different from those of

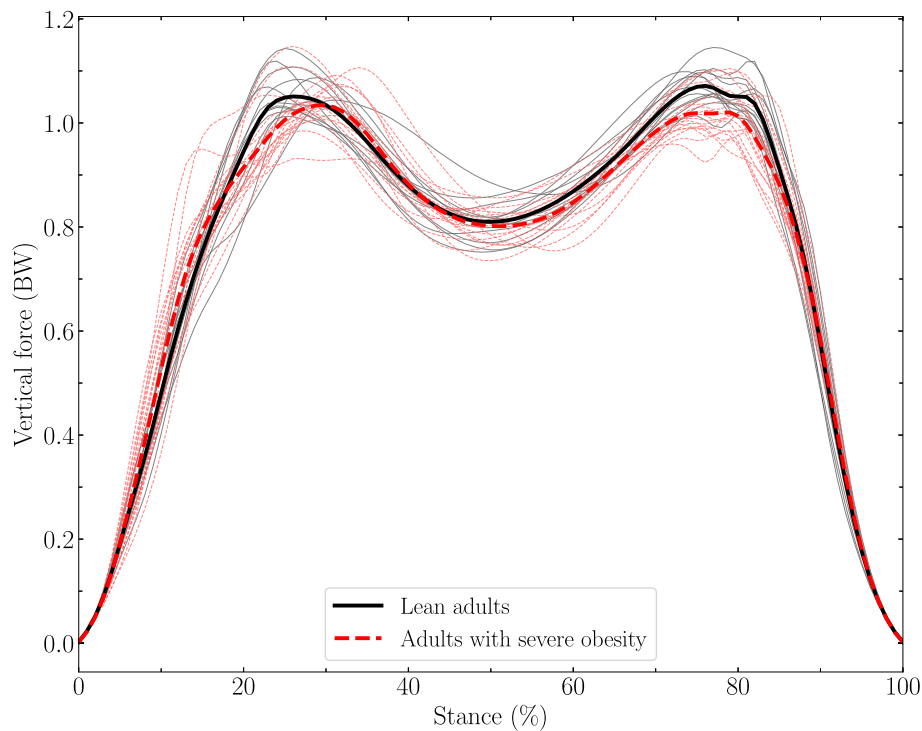


Fig. 3. Relative vertical ground reaction force signal [expressed in body weight (BW)] during stance and for all participants within lean adults (dashed red line) and adults with severe obesity (solid black line) and the overall average curve (thicker dashed red and solid black lines) for both groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

lean adults indicating a greater relative mediolateral force during most of the stance. However, similar magnitudes of the relative anterior-posterior and vertical forces during stance were reported for individuals with severe obesity compared to lean adults. This absence of modification in the relative anterior-posterior force seem to be specific to severe obesity because they are different from those previously found in adults with overweight and class I obesity (Kim et al., 2022). Therefore, increasing the level of obesity accentuates the difference in relative mediolateral force but promotes no specific modifications in relative anterior-posterior force likely due to chronic loading adaptation. Further studies are warranted to examine if there are gradual or discontinuous changes in relative anterior-posterior force with increasing levels of obesity.

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Author contributions

Conceptualization, A.P., A.F.M., and D.M.; methodology, A.P., A.F.M., and D.M.; investigation, A.F.M. and D.M.; formal analysis, A.P.; writing—original draft preparation, A.P.; writing—review and editing, A.P and D.M.; supervision, D.M.

Availability of data and material

The datasets supporting this article are available on request to the corresponding author.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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