TITLE: Longitudinal changes in fat mass and the hippocampus.

RUNNING TITLE: Changes in fat mass and the hippocampus.

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FUNDING: A. Ambikairajah was supported by an Australian Government Research Training Program (AGRTP) Domestic and Fee-Offset Scholarships. The rest of the authors have nothing to disclose.

DISCLOSURE: The authors declared no conflict of interest.

WORDS IN MANUSCRIPT: 3980 **TABLES:** 3

WORDS IN ABSTRACT: 199 **FIGURES:** 2

KEY WORDS: Adiposity; hippocampus; body mass index; waist circumference; waist-hip ratio.

WHAT IS ALREADY KNOWN?

- In addition to being associated with a number of deleterious health and wellbeing outcomes including, type II diabetes mellitus, cancer and cardiovascular disease, overweight BMI in midlife confers a 35% increased risk of developing Alzheimer's disease (AD), compared with normal BMI.

STUDY IMPORTANCE

- Our findings indicate that the detrimental effects of overweight/obesity on the neurological health of individuals may extend beyond the duration of overweight/obesity itself.
- The clinical translation of our research findings is important to ensure that possible populations at risk of poor neurological health are not overlooked, and instead, targeted intervention programs are developed to mitigate identified risks.

ABSTRACT

OBJECTIVES: To investigate cross-sectional and longitudinal associations between fat mass i.e. body mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WTHR) and hippocampal volumes (HVs).

METHODS: UK Biobank participants (n = 20395) aged 40-70 (mean follow-up = 7.66 years), were included and categorised into one of four groups, which represented their baseline fat mass status and trajectory of change by follow-up assessment i.e. normal to overweight/obese (NO), overweight/obese to normal (ON), normal stable (NS) or overweight/obese stable (OS). Regression models used NS (i.e. WC: < 80 cm in women and < 94 cm in men; WTHR: < 0.85 in women and < 0.90 in men and BMI: < 25 kg/m^2 in women and men), as the reference group. HVs were automatically segmented using FMRIB Software Library.

RESULTS: Compared to NS, OS (BMI: B = -62.23, standard error [SE] = 16.76; WC: B = -145.56, SE = 16.97 and WTHR: B = -101.26, SE = 19.54) and ON (BMI: B = -61.1, SE = 30.3; WC: B = -93.77, SE = 24.96 and WTHR: B = -69.92, SE = 26.22) had significantly lower HVs.

CONCLUSIONS: The detrimental effects of overweight/obesity may extend beyond the duration of overweight/obesity itself.

INTRODUCTION

The prevalence of overweight and obesity has accelerated in recent decades, with current global estimates indicating that the proportion of adults with a body mass index (BMI) greater than 25 kg/m^2 (i.e. overweight) is one in three (1, 2). These findings are of particular importance within the context of our globally ageing population given that previous research has demonstrated that, in addition to being associated with a number of unfavourable health and wellbeing outcomes including, type II diabetes mellitus, cancer and cardiovascular disease (3), overweight BMI in midlife confers a 35% increased risk of developing Alzheimer's disease (AD), compared with normal BMI (4).

The hippocampus is a brain region which is sensitive to changes, particularly in the early stages of neurodegeneration (5–7). Notably, the accumulation of fat tissue, particularly visceral fat, which is often prevalent in individuals with overweight/obesity is known to be closely linked with elevated levels of pro-inflammatory cytokines (8–10), which have been associated with smaller hippocampal volumes (11). In animal models, obesity in ageing is associated with a heightened state of systemic inflammation, which exacerbates blood brain barrier disruption, neuroinflammation and oxidative stress in the mouse hippocampus (12). These pathophysiological consequences of overweight/obesity have been closely linked with impaired hippocampal integrity in humans (11, 13). Interestingly, a post-mortem study of non-demented elderly individuals revealed that those with obesity had neuropathological hallmarks of AD, such as higher levels of hippocampal amyloid-beta peptides, amyloid precursor protein and hyperphosphorylated tau protein, compared with those without obesity (14). However, neuroimaging studies have revealed that the association between fat mass and hippocampal volume in middle to early-old aged adults has been less consistent with studies reporting negative (15–18), positive (19) or no association (20–22).The heterogeneous results may be explained by the typical use of BMI, which does

not precisely index changes in visceral fat and is inherently biased by the ageing process (23). Therefore, other cost-effective, feasible and useful clinical measures, including waist circumference (WC) and/or waist-to-hip ratio (WTHR) may be better suited for representing changes in visceral fat. Critically, objectively measured longitudinal changes in WC and WTHR have not been adequately investigated in previous studies that have examined the relationship between fat mass and hippocampal volume (12, 16, 17, 24).

The current study aimed to rectify these shortcomings by investigating the associations between fat mass (i.e. BMI, WC and WTHR) and changes in fat mass over time with hippocampal volumes in middle to early-old aged women and men. Secondary aims were to determine (1) whether these associations differed between measures of fat mass and (2) which measure(s) of fat mass were most strongly associated with total body fat and visceral fat as measured by the gold standard tool, dual-energy x-ray absorptiometry (DEXA). It was hypothesised that any observed associations between fat mass and the hippocampus would be dependent on i) baseline fat mass status (i.e. normal, overweight or obese), ii) the trajectory of change and iii) the measure of fat mass used. It was predicted that individuals who were classified as chronically overweight/obese (and thereby experience chronic, low grade systemic inflammation as well as other comorbidities), would have lower hippocampal volumes than those who progressed from normal weight to overweight/obese categories, or maintained their weight within the normal range. Furthermore, it was hypothesised that these results would be best represented by the fat mass measure which was most suited for indexing changes in visceral fat.

METHODS

Participants

A total of 502536 participants aged 37-73 years at baseline (2006 - 2010) were from the UK Biobank study (25) and considered for inclusion. Participants were recruited from the National Health Service central registers. Of those considered, as a minimum requirement, only those who had completed a structural MRI scan (21390) and had a measure of BMI, WC and hip circumference (HC) at baseline and follow-up assessment (2014 +) were included (20849). After excluding participants with neurological disorders, including stroke (n = 256) or those who were underweight i.e. BMI <18.5 kg/m^2 (n = 179), or had extreme obesity i.e. BMI > 50 kg/m^2 (n = 20), 20395 participants remained for analysis in the present study. None of the included participants had dementia.

Fat mass measures

BMI, WC and WTHR were measured at baseline, first follow-up assessment and second follow-up assessment (Figure 2). Trained staff used standardised procedures to obtain body size measurements. Participants were asked to remove shoes, socks and heavy outer clothing before body weight was measured with the Tanita BC-418 MA body composition analyser (Tanita, Tokyo, Japan) and standing height was measured using a Seca 202 height measure (Seca, Hamburg, Germany). BMI was calculated with the formula: weight (kg) / height^2 (m^2). WC was measured with a Wessex non-stretchable sprung tape measure (Wessex, United Kingdom) at the level of the umbilicus, while HC was measured at the widest point. WTHR was computed (i.e. WC (cm) / HC (cm)). Total body fat and visceral fat was measured (for 4482 and 4431 participants respectively) using a dual-energy x-ray absorptiometry

(DEXA) device, specifically, the GE-Lunar iDXA (GE Healthcare, Chicago, Illinois, Unites States of America)

Of the 20395 participants included in the study, 5080 had an additional follow-up measure of fat mass (Figure 2). For these participants, annual changes in fat mass was calculated with the formula:

$$y = B_0 + B_1 \text{follow-up (years)}$$

Where B_0 is the fat mass at each timepoint and B_1 is the annual change in fat mass.

For each measure of fat mass, participants were then categorised into one of four groups, which represented their baseline fat mass status and their trajectory of change by follow-up assessment i.e. normal to overweight/obese (NO), overweight/obese to normal (ON), normal stable (NS) or overweight/obese stable (OS). Standardised criteria from the International Diabetes Federation (26) and the World Health Organization (27, 28) were used to classify normal and overweight/obese groups. Specifically, BMI for men and women: overweight/obese >= 25 kg/m^2, normal < 25 kg/m^2; WC for women: overweight/obese >= 80 cm, normal < 80 cm; WC for men: overweight/obese >= 94 cm, normal < 94 cm; WTHR for women: overweight/obese >= 0.85, normal < 0.85 and WTHR for men: overweight/obese >= 0.90, normal < 0.90.

Covariates

Covariates included sex, follow-up period, self-reported age and educational attainment, vascular/heart problems (i.e. heart attack, angina or hypertension) and diabetes, diagnosed by doctor. Participants were classified as having hypertension if they were using blood pressure medication and also, as having diabetes if they were using oral anti-diabetic medication or insulin. Further covariates included self-

reported physical activity (i.e. number of days per week spent doing at least 10 minutes of continuous vigorous activity), smoking (i.e. ever or never) and frequency of alcohol intake.

Image acquisition

Magnetic resonance imaging (MRI) scans were acquired at the second follow-up assessment (Figure 2). All participants were imaged across three imaging centres with identical scanners (3T Siemens Skyra; software platform VD13) using a 32-channel head coil (29). T1-weighted images were acquired in the sagittal orientation using a 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence over a duration of 5 minutes; resolution = 1 x 1 x 1 mm; field of view = 208 x 256 x 256 matrix (29).

Segmentation and image analysis

Images were processed and analysed by the UK Biobank imaging team using FMRIB Software Library (FSL) v6.0 (http://fsl.fmrib.ox.ac.uk/fsl). More detailed information on the standard MRI analysis protocols have been reported elsewhere (29, 30), however, we have included an overview of key steps. The UK Biobank processing pipeline included a linear and then non-linear registration to a 1mm resolution version of the MNI152 template. Automated tissue segmentation was conducted and subcortical structures, such as the hippocampus, were modelled. Raw hippocampal volumes were multiplied by the overall volumetric head-size scaling factor to obtain normalised volumes, which were subsequently used for all analyses.

Statistical methods

All statistical analyses were conducted using R (version 3.6.1), in RStudio (version 1.1.419). Pearson's correlation coefficients were used to measure the strength of the associations between BMI, WC, WTHR and DEXA measurements of total body fat and visceral fat. Multiple linear hierarchical regression models were then computed to quantify the association between fat mass and changes in fat mass and hippocampal volumes, while controlling for age and sex (Model 1). Model 2 further controlled for education, vascular/heart problems, diabetes, physical activity, smoking and alcohol use. Analysis which investigated the associations between fat mass categories (i.e. NO, ON, NS and OS) and the hippocampus also adjusted for length of follow-up (years). Within each fat mass category, longitudinal changes in fat mass and the hippocampus were assessed. Since the fat mass thresholds for categorisation differed between men and women (particularly for WC and WTHR), these analyses were repeated separately. Both unstandardised beta-coefficients and annual percentage change in fat mass were utilised in the reporting and interpretation of results, where appropriate. Annual percentage change was calculated by dividing the annual change in fat mass by the baseline fat mass, multiplied by 100. The alpha level was set at < 0.05. Non-linear associations were explored by fitting a squared term for fat mass. Assumptions of linearity, including homoscedasticity and normality of residuals were examined.

RESULTS

The participants' demographic and health characteristics are presented in Table 1. Differences between those who were included and excluded have been reported in Supplementary Table 1. For those included, participants were on average 54.86 years (standard deviation [SD] = 7.48) with a mean follow-up of 7.66 years (SD = 1.42) at baseline. The average total hippocampal volume was 7709.73mm^3, (SD = 867.92mm^3). On average, participants lost 68.6 grams/year over the follow-up period. Boxplots of fat mass change over the follow-up between NS, NO, OS and ON groups are presented in Figure 1.

Demographic information for NS, NO, OS and ON groups for each fat mass measure are presented in Supplementary Tables 2-4.

Cross-sectional analyses revealed that after adjusting for all covariates, higher BMI, WC and WTHR were each individually associated with lower hippocampal volumes (Supplementary Table 5; BMI: B = -9.61, standard error [SE] = 1.77; WC: B = -6.74, SE = 0.69 and WTHR: B = -690.78, SE = 119.13).

Overall, longitudinal changes in continuous BMI, WC or WTHR were not significantly associated with lower hippocampal volumes (Supplementary Table 6), however, compared to participants who were NS for BMI, WC or WTHR, those who remained OS (BMI: B = -62.23, SE = 16.76; WC: B = -145.56, SE = 16.97 and WTHR: B = -101.26, SE = 19.54) or were ON (BMI: B = -61.1, SE = 30.3; WC: B = -93.77, SE = 24.96 and WTHR: B = -69.92, SE = 26.22) had significantly lower hippocampal volumes across all three measures of fat mass (Table 2). Participants who were NO for WC or WTHR also had significantly lower hippocampal volumes than those who were NS (WC: B = -74.39, SE = 25.51 and WTHR: B = -62.09, SE = 22.52). However, participants who were NO for BMI had no significant difference in hippocampal volume compared to those who were NS.

Analyses were repeated separately for women and men (Supplementary Tables 7 and 8). For men, OS (BMI: B = -92.17, SE = 26.55; WC: B = -206.02, SE = 25.69 and WTHR: B = -114.98, SE = 29.08) and ON (BMI: B = -97.79, SE = 45.76; WC: B = -91.18, SE = 34.5 and WTHR: B = -96.29, SE = 40.49) groups were consistently associated with lower hippocampal volumes compared with NS across all measures of fat mass. However, no significant differences in hippocampal volumes were consistently found between the NO and NS groups. For women, OS groups had consistently lower hippocampal volumes than NS across all measures of fat mass (BMI: B = -45.19, SE = 21.52; WC: B = -101.73, SE = 22.5 and WTHR: B = -70.54, SE = 28.67). For WC and WTHR, the NO group had lower hippocampal

volumes than the NS group (WC: B = -84, SE = 32.43 and WTHR: B = -103.79, SE = 28.43), however, these differences were not found for BMI. ON participants had significantly lower hippocampal volumes compared to the NS group for WC (B = -113.16, SE = 36.51), however, this difference was not observed for WTHR or BMI.

For each individual subgroup (i.e. NS, NO, OS, ON), annual change in BMI, WC or WTHR had no significant association with hippocampal volume (Supplementary Table 9). This was consistently observed between women and men (Supplementary Tables 10 and 11).

As seen in Table 3, WC was most correlated with visceral fat (r = 0.83), compared to WTHR (r = 0.73) and BMI (r = 0.69). However, BMI was most correlated with total body fat (r = 0.90), compared to WC (r = 0.72) and WTHR (r = 0.29).

DISCUSSION

This study aimed to investigate the association between fat mass and longitudinal changes in fat mass with hippocampal volumes in middle to early-old aged women and men. To better understand these relationships, the current study also aimed to determine whether observed associations differed between measures of fat mass and to identify which measure(s) of fat mass were most strongly associated with total body fat and visceral fat, as indicated by DEXA. The key findings were that (1) WC was most strongly correlated with visceral fat (r = 0.83), compared to WTHR (r = 0.73) and BMI (r = 0.69), (2) individuals with chronic overweight/obesity had significantly lower hippocampal volumes (specifically, WC: 1.13%; WTHR: 0.79% and BMI: 0.49% smaller after adjusting for all covariates) when compared with those who maintained a normal level of fat mass (i.e. WC: < 80 cm in women and < 94 cm in men; WTHR: < 0.85 in women and < 0.90 in men and BMI: < 25 kg/m^2 in women and men) at baseline and

follow-up (average follow-up = 7.66 years) and (3) individuals who were within a normal range of fat mass at follow-up assessment, yet were previously classified as having overweight/obesity at baseline had lower hippocampal volumes than those who remained normal stable (specifically, WC: 0.73%; WTHR: 0.55% and BMI: 0.48% smaller after adjusting for all covariates). Notably, the significant cross-sectional association between fat mass and hippocampal volume was not previously detected in a study on the same cohort (18). In that particular study, the sample was half the size of the present study and depression was also considered as a covariate. Our analysis did not include depression as a covariate, partly due to the significant degree of missingness present. The current findings emphasise the importance of maintaining normal weight for neurological health and also suggest that the detrimental effects of overweight/obesity may extend beyond the duration of overweight/obesity itself.

Overweight/obesity is a complex condition which has multifactorial components (including genetic, environmental and socioeconomic factors) that underlie its aetiology. The current findings further highlight the complexity of overweight/obesity by emphasising the long term impact the condition may have on the neurological health of individuals. There are a number of possible biological mechanisms, which may explain the consistent finding that those who were OS or ON had lower hippocampal volumes than those who were NS, across all measures of fat mass. For example, previous studies have demonstrated that the accumulation of fat tissue, particularly visceral fat, is closely linked with elevated levels of pro-inflammatory cytokines (19-21), which have been associated with smaller hippocampal volumes (22). This is of particular importance as the current results revealed that (1) WC was most strongly associated with visceral fat and (2) the largest effect was consistently found for WC, as those who were OS and ON had 1.13% and 0.73% smaller hippocampal volumes than NS for WC, respectively, compared with WTHR (OS: 0.79% and ON: 0.55% smaller hippocampus than NS) and BMI (OS: 0.49% and ON: 0.48% smaller hippocampus than NS). Notably, no statistical differences

between NS and NO groups were found for BMI, which was lowly correlated with visceral fat levels compared to WC but was most highly correlated with total body fat, yet, for both WC and WTHR the NO group had significantly lower hippocampal volumes than NS (0.58% and 0.49 % smaller respectively).

Taken together, the current findings seem to suggest that an accumulated burden of pathology may have developed in those that were OS, ON and NO, perhaps as a result of chronic, low grade systemic inflammation that persists, commonly in individuals with overweight/obesity (due to an accumulation of visceral fat tissue), or other pathological mechanisms, resulting in lower hippocampal volumes compared to those who maintained a normal level of fat mass. This is consistent with the literature which has shown that chronic obesity is associated with a cascade of potentially harmful physiological processes (including oxidative stress, inflammation and insulin resistance) which are implicated in the deterioration of metabolic homeostasis (31), and has been linked with accelerated neurodegeneration (32). Furthermore, previous research has demonstrated that individuals who gained weight, lost weight or remained obese had an increased risk of mortality compared with those who maintained normal amounts of body fat (33). Therefore, these results appear to indicate that it is the chronicity of overweight/obesity which is associated with lower hippocampal volumes. However, an alternative explanation is that, for reasons not well understood, those who were ON or OS had lower hippocampal volumes at baseline. Whilst possible, this explanation is less likely given the substantial amount of evidence in the literature that has demonstrated the link between obesity and neurodegeneration (4, 34, 35), which also aligns with experimental data in animals showing that obesity in mice can lead to decreased neurogenesis and accelerated neurodegeneration, resulting in dementia pathology (36, 37). Nevertheless, it cannot be completely discounted that factors, such as sampling bias, may be present and future research should investigate this further.

The use of BMI, WC and WTHR enabled the comparison of results across three commonly used clinical measures/indices of fat mass. Whilst more precise technology for measuring fat mass exists, such as DEXA and MRI (38), these tools require relatively large investments of time, money and resources, compared to BMI, WC and WTHR. Furthermore, longitudinal measures of fat mass using DEXA or MRI are currently not available in the UK Biobank dataset. As a result, an important question raised by these findings is which clinical measure (i.e. BMI, WC or WTHR) best represents the association between fat mass and the hippocampus and may therefore be a better predictor of future neurodegeneration. Firstly, as previously noted, correlation analysis indicated that WC was most strongly associated with visceral fat ($r = 0.83$), compared to WTHR ($r = 0.73$) and BMI ($r = 0.69$). This may provide a theoretical rationale for its use as a clinical measure to assess the association between fat mass and the hippocampus. Furthermore, subgroup analysis in women revealed statistically significant differences between NO, OS, ON groups and those who were NS for WC, however, these differences were not consistently found for WTHR and BMI (Supplementary Table 7). Several possible reasons may account for these findings. For example, previous research has demonstrated that women tend to accumulate central fat (specifically visceral fat), during midlife (39), which may explain the observed associations, given that WC was most strongly correlated with visceral fat, which has been previously linked to neurodegeneration through the elevation of pro-inflammatory cytokines (22). Another possibility is that the individuals who were in each fat mass group (i.e. NS, NO, OS and ON) varied to a certain degree between measures due to the differences with the standardised cutoff points used for categorisation. Therefore, the observed differences in results may reflect the sensitivity of the fat mass thresholds for each category (i.e. NS, NO, OS and ON) to better capture individuals who had healthier hippocampal volumes than others. To assess this, post-hoc analysis was conducted whereby a fifth group was established, which included individuals ($n = 3998$) who were consistently normal stable for all of BMI, WC and WTHR (henceforth called consistently normal stable i.e. CNS). Interestingly, for

WC, no difference was found between those who were NS or CNS. Furthermore, the magnitude and significance of effects remained consistent between NS and NO, OS and ON groups with and without the inclusion of a CNS group (Supplementary Table 12). Alternatively, for WTHR and BMI the CNS group had significantly larger hippocampal volumes than those who were NS. Furthermore, the differences between ON and OS groups with NS for BMI were no longer detected once the CNS group was included. A similar result was observed for the ON and NO groups for WTHR. Therefore the CNS group was likely capturing the individuals with larger hippocampal volumes for BMI and WTHR, but not WC. This may be because BMI and WTHR measures reflect body size and on average head size, which is itself associated with hippocampal volume. These findings seem to further demonstrate the robustness and sensitivity of WC for assessing the relationship between visceral fat and hippocampal volume. Taken together, these results align with and extend upon previous studies, which have noted that WC is a more sensitive indicator for determining the adverse effects of overweight and obesity on brain health than BMI, particularly in females (40).

Strengths and limitations

Key strengths of the current study include (1), the large cohort of middle to early-old aged adults (specifically 20395 individuals) that included both men and women, (2) the use of longitudinal changes in fat mass and (3), the use of multiple commonly used clinical measures/indices of fat mass (including BMI, WC and WTHR) to address the questions of interest. Furthermore, due to the large sample size, a large number of relevant covariates could be adjusted for (including age, sex, follow-up period, educational attainment, vascular/heart problems i.e. heart attack, angina or hypertension, diabetes, physical activity, smoking and alcohol intake), which ensured that observed associations were unlikely driven by common comorbid conditions that are often associated with obesity, such as diabetes, hypertension and physical activity levels. Notably, previous studies that have examined longitudinal

changes in fat mass with hippocampal volumes in middle to early aged adults have been limited by sample size (12, 16, 17). Two of the three studies used BMI as their only measure of fat mass (16, 17), one of which, focused on a sample consisting only of men (16), whereas the other used self-reported BMI (12) and the third estimated BMI and WC in participants at age 50 (17). Given this, the current study is unique in its ability to directly measure, assess and discuss the temporal association between longitudinal changes in BMI, WC and WTHR, with the hippocampus, within a large cohort of both men and women.

A limitation of the current study is that imaging data was only available at one timepoint (Figure 2). Therefore, it is difficult to determine whether other age related factors could be responsible for the observed differences or, as previously discussed, whether these differences were already present a baseline. For example, if smaller hippocampal volumes were observed at baseline and were associated with longitudinal increases in adiposity, then these findings may highlight a predisposed vulnerability to external food cues driving eating behaviour. Furthermore, clear standardised thresholds for WC and WTHR that separate overweight and obese groups do not currently exist. This limited the ability to identify possible differences that may exist between overweight and obese participants for WC and WTHR. Additionally, healthy participation bias for the UK Biobank cohort indicates that these findings may not be completely representative of the broader population and require replication in other datasets (41). Our study was limited to the association between changes in fat mass and the brain, however, future studies would benefit from investigating whether the observed results translate to differences in cognitive performance, particularly in domains related to the hippocampus, such as learning and memory.

CONCLUSION

The current findings emphasise the importance of maintaining normal weight for neurological health and also suggest that the detrimental effects of overweight/obesity may extend beyond the duration of overweight/obesity itself.

Acknowledgements

We would like to acknowledge and thank all UK Biobank participants and the UK Biobank team for their work.

Data sharing

This research has been conducted using the UK Biobank resource under application number 47813. Researchers can apply to use the UK Biobank resource and access the data used. No additional data are available.

Ethical Approval

UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (REC reference: 11/NW/0382). All participants gave written informed consent before enrolment in the study, which was conducted in accordance with the principles of the Declaration of Helsinki.

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Figure Legends:

Figure 1 Fat mass change over follow-up for each group. Abbreviations: NS, Normal stable; NO, Normal to overweight/obese; OS, Overweight/obese stable; ON, Overweight/obese to normal.

Figure 2 Timeline of UK Biobank study. Abbreviations: BMI, Body Mass Index; WC, Waist Circumference; WTHR, Waist to Hip Ratio; SD, Standard Deviation.