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Perceived weight discrimination and 10-year risk of allostatic load among US adults

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ABSTRACT

Background: Discrimination promotes multi-system physiological dysregulation termed allostatic load, which predicts morbidity and mortality. It remains unclear whether weight-related discrimination influences allostatic load.

Purpose: To prospectively examine 10-year associations between weight discrimination, allostatic load, and its components among adults 25-75y in the Midlife Development in the US Biomarker Substudy.

Methods: Participants with information on weight discrimination were analyzed (n=986). At both timepoints, participants self-reported the frequency of perceived weight discrimination across nine scenarios as 'never/rarely' (scored as 0), 'sometimes' (1), or 'often' (2). The two scores were averaged and then dichotomized as 'experienced' versus 'not experienced' discrimination. High allostatic load was defined as having ≥3 out of 7 dysregulated systems (cardiovascular, sympathetic/parasympathetic nervous systems, hypothalamic pituitary axis, inflammatory, lipid/metabolic, and glucose metabolism), which collectively included 24 biomarkers. Relative risks (RR) were estimated from multivariate models adjusted for socio-demographic and health characteristics, other forms of discrimination, and BMI.

Results: Over 41% of the sample had obesity, and 6% reported weight discrimination at follow-up. In multivariable-adjusted analyses, individuals who experienced (versus did not experience) weight discrimination had twice the risk of high allostatic load (RR: 2.07, 95%CI: 1.21, 3.55 for baseline discrimination; 2.16, 95%CI: 1.39, 3.36 for long-term discrimination). Weight discrimination was associated with lipid/metabolic dysregulation (1.56, 95%CI: 1.02, 2.40),

glucose metabolism (1.99, 95% CI: 1.34, 2.95), and inflammation (1.76, 95% CI: 1.22, 2.54), but no other systems.

Conclusions: Perceived weight discrimination doubles the 10-year risk of high allostatic load. Eliminating weight stigma may reduce physiological dysregulation, improving obesity-related morbidity and mortality.

Word Count: 250

Key Words: obesity stigma, weight discrimination, allostatic load, allostasis, dysregulation, weight stigma

INTRODUCTION

Obesity is the leading contributor to disability-adjusted life-years in the US, at least partly due to its adverse effects on multiple health outcomes (1). It is well-established that obesity etiology is both complex and manifold (2), suggesting a need for integrated biopsychosocial and biomedical approaches to address it (3). Despite this, predominant approaches to treat obesity continue to accentuate the role of the individual (4), unintentionally contributing to a cycle that further entrenches obesity and its related health consequences by promoting stigmatization of this condition (3, 4).

Research suggests that pervasive individually-targeted health campaigns increase public prejudice toward individuals with obesity by increasing the perception of obesity as a lifestyle choice resulting from weakness of character (5). A downward consequence of this perception is increased weight-related stigma, and often, discrimination (6, 7). Weight discrimination is the fourth most prevalent form of discrimination among adults, after age, sex, and race-based discrimination (8). Between 1995 and 2006, the absolute prevalence of weight discrimination increased from 7% to 12% in the US, representing a 66% increase in prevalence and exceeding the proportion that could be attributed to concomitant increases in obesity (9). Despite the lay belief that weight stigma motivates positive behavioral change (10), most evidence demonstrates that weight shaming promotes poorer dietary and exercise practices and health care avoidance (11, 12), akin to how experienced racism correlates with negative health outcomes like cancer risk (13, 14). As such, weight discrimination may contribute to obesity (3, 15) by discouraging individuals from seeking treatment, reducing engagement with social support, or promoting disordered eating patterns, less healthful food choices, and emotional dysregulation (12, 16-21). Furthermore, weight stigma has been directly linked to overeating and physical inactivity in

randomized controlled trials (10), providing plausible mechanisms through which weight stigma promotes physiologic dysregulation.

Discrimination also affects chronic stress, which could subsequently promote adverse physiologic changes (3, 15, 22-24). For example, weight stigma has been associated with higher glycemic parameters (24) and C-reactive protein (CRP) (15) in large, longitudinal studies. In studies where weight stigma was experimentally manipulated, greater stigmatization resulted in sustained cortisol secretion (22, 25). These findings echo existing research on the effects of perceived discrimination on allostatic load (26, 27), suggesting that there may be a similar connection between weight discrimination and physiologic dysregulation.

Allostatic load refers to the cumulative adverse adaptation of multiple physiological systems (i.e. cardiovascular, sympathetic, parasympathetic, metabolic, etc.) in response to chronic stressors, which has been more strongly associated with chronic disease morbidity and mortality than traditional risk markers (28, 29). Although the operational definitions of allostatic load vary across studies (28), the allostatic load metric is considered a robust estimator of multi-system dysregulation in population studies (30). While it is valuable to examine allostatic load as a composite score, examining dysregulation within the individual allostatic load systems can help identify underlying pathways through which the allostatic load response is manifested, according to the population's specific characteristics (30). As such, we examined whether the chronic stress associated with weight discrimination impacts both allostatic load and seven individual systems used to define allostatic load to elucidate the underlying pathways through which weight discrimination promotes dysregulation.

We propose that weight-related discrimination triggers multi-system dysregulation that adversely affects other health outcomes (e.g. cardiovascular disease) beyond the effects of

obesity alone (**Figure 1**). Similar to the cyclic obesity/weight-based stigma (COBWEBS) model (3), weight-related discrimination is characterized as a stressor that triggers a downward cascade of unfavorable psychosocial and behavioral processes that ultimately result in poor biological outcomes across multiple systems (e.g. metabolic syndrome, cardiovascular disease) (31, 32). To test this hypothesis, we used unique data from the national survey of Midlife Development in the US (MIDUS) study to prospectively examine the 10-year associations between perceived weight discrimination and allostatic load among adults ages 25-74y.

METHODS

Participants

We used data from the MIDUS I (1995-1996), MIDUS II (2004-2006), and MIDUS Biomarker Substudy (2004-2009) to examine associations between perceived weight discrimination, allostatic load, and the individual systems comprising allostatic load. Detailed information about the study's sampling procedures have been previously published (33). Briefly, 7,108 non-institutionalized adults (including 950 siblings and 1,914 twins) aged 25-74y participated in a telephone survey conducted via random digit dialing in 1995-1996. At follow-up between 9 and 10 years later, approximately 4,900 members of the original cohort responded to an additional phone survey; the mortality-adjusted longitudinal response rate at MIDUS II was 75%. During the 10-year follow-up, a subset of 1,255 adults who completed the phone interview and questionnaires were randomly selected and invited to participate in a biomarker substudy. The present analysis includes those in the biomarker sub-study with sufficient information to compute allostatic load (n=1,233) or the individual allostatic load systems (n=1,158-1,254) and who had information on perceived weight discrimination (n=986).

Perceived Weight Discrimination

Participants self-reported instances of perceived discrimination within interpersonal relationships on a day-to-day basis at both the baseline and 10-year follow-up survey. Nine scenarios about interpersonal discrimination were queried with the question 'How often on a day-to-day basis do you experience each of the following types of discrimination?' The scenarios included: 'you are treated with less courtesy than other people', 'you are treated with less respect than other people', 'you receive poorer service than other people at restaurants or stores', 'people act as if they are afraid of you', 'people act as if they think you are dishonest', 'people act as if they think you are not as good as they are', 'you are called names or insulted', and 'you are threatened or harassed'. The frequency categories for these scenarios included 'Often', 'Sometimes', 'Rarely', or 'Never'. These questions were initially developed for a study examining racial discrimination, and have been used widely since then (34).

Similar to Puhl and others (8), only participants reporting discrimination 'Sometimes' or 'Often' were counted as instances of discrimination. We constructed a continuous measure of perceived discrimination that allocated 2 points for every instance that a discrimination scenario was reported as 'Often', 1 point for every scenario reported as 'Sometimes', and 0 points for those who reported discrimination 'Rarely' or 'Never'. Separately, participants were asked to select the primary reason(s) for discrimination, from among the following options: age, gender, race, height or weight, ethnicity or nationality, physical disability, some aspect of appearance other than weight or height, sexual orientation, religion, and other reason. Like previous studies, we refer to the 'height or weight' variable as 'weight discrimination' throughout the manuscript (8).

We constructed two variables for perceived weight discrimination at both baseline and 10-year follow-up. First, a continuous measure of perceived weight discrimination was computed from the continuous perceived discrimination score for individuals who reported 'weight' as a primary reason for discrimination. The observed range for this score was 0-10 at baseline and 10-year follow-up. Secondly, a categorical indicator variable was created for individuals who experienced any vs. no perceived weight discrimination.

Individuals who reported no instances of discrimination received a weight discrimination score of 0 (n=126). We also carried baseline values forward for non-responders at the 10-year follow-up who reported discrimination related to weight at baseline based on the correlation between these two measures (n=215, r=0.40, p<0.0001). Individuals who refused to respond to the question or whose responses were deemed 'inappropriate' by study administrators were coded as missing (n=46). Complete information was available for 986 participants at baseline and 940 at follow-up. The two exposures of interest were baseline weight discrimination and long-term weight discrimination. Long-term discrimination was computed as the average value of perceived discrimination at baseline and at 10-year follow-up or as discrimination at 10-years for individuals with missing baseline data.

Allostatic Load

Allostatic load was comprehensively measured and defined in accordance with previous studies conducted within this population using a score that captured dysregulation across seven systems, including the sympathetic and parasympathetic nervous systems, hypothalamic pituitary adrenal (HPA) axis, cardiovascular functioning, lipid and general metabolic activity, glucose metabolism, and inflammatory system(31, 35, 36) (**Table 1**). All physiologic measures were

collected during the Biomarker Substudy visit, which corresponded with the timing of the 10-year follow-up exam.

Sympathetic nervous system functioning was measured with 12-hour overnight urinary measurements of epinephrine and norepinephrine via high-pressure liquid chromatography, and levels were reported per level of creatinine (g). Parasympathetic nervous system activity was measured by four heart rate variability parameters during an 11-minute seated rest period using an electrocardiograph: low frequency spectral power, high frequency spectral power, the standard deviation of heartbeat to heartbeat intervals, and the root mean square of successive differences. Overnight urinary cortisol and serum dehydroepiandrosterone sulfate (DHEA-S) were used as markers of HPA activity. Markers of cardiovascular functioning included resting systolic blood pressure (SBP), heart rate, and pulse pressure. Lipid/fat metabolism markers included high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, body mass index (BMI), and waist-to-hip ratio (WHR). Glycosylated hemoglobin (HbA1c), fasting glucose, and the homeostasis model of insulin resistance (HOMA-IR) were used to assess glucose metabolism. Inflammation was measured with plasma CRP, fibrinogen, serum interleukin-6 (IL6), the soluble adhesion molecule E-selectin, and intracellular adhesion molecule-1. All blood, urine, saliva, cardiovascular, and heart rate variability measurements were collected during an overnight stay at one of three University General Clinical Research Centers. Detailed collection protocols for each biomarker have been previously published (31, 37). Consistent with previous studies (36), we computed a system risk score for each of the seven systems that was in the upper or lower quartile of the biomarker population-specific distribution, based on whether high or low values of the parameter were generally associated with higher health risk. Additionally, consistent with previous research (35, 38-40), participants who

196 reported using medications to treat dysregulated parameters were categorized as high risk for that
197 parameter to account for pre-existing dysregulation. These medications included
198 antihypertensive medications for high SBP; heart rate-reducing medications (e.g. beta-blockers
199 and atrio-ventricular nodal blockers) for high resting heart rate; hypoglycemic agents for
200 dysregulated fasting glucose and HbA1c; statins, cholesterol absorption inhibitors, niacin and/or
201 bile acid sequestrants for dysregulated LDL; fibrates for elevated serum triglycerides;
202 testosterone for dysregulated DHEA-S, and anti-inflammatory medications (including non-
203 steroidal anti-inflammatory medications) for dysregulated CRP and IL-6. The number of
204 participants with dysregulated parameters including and excluding medication data in the
205 definition of allostatic load is shown on **Supplemental Table 1**. In sensitivity analyses, we
206 examined all associations excluding the use of medications in the definitions of system
207 dysregulation.

208 System risk scores were continuous and computed by calculating the proportion of
209 individual biomarkers within the system that were dysregulated. Scores could range from 0 to 1
210 (corresponding with 0-100% of system biomarkers in high-risk range). We only computed
211 system risk scores for participants with values for at least half of the system's biomarkers. Over
212 90% of participants had information for all 7 systems, and most participants (98%) had complete
213 data for all systems excluding the parasympathetic measures; 106 participants (8%) were missing
214 information on the parasympathetic parameters due to instrumentation failures and/or
215 measurement difficulties.

216 The allostatic load variable was computed for participants with data on at least six of the
217 seven systems by summing the seven system risk scores; total allostatic load scores ranged from
218 0 to 7, with higher scores indicative of more dysregulation. An indicator variable for high versus

low allostatic load was created: allostatic load summary scores ≥3 were considered "high" and scores <3 were considered "low." Although the median allostatic load score in this population was 2, using a higher cut-point allowed us to capture individuals at higher disease risk (39).

Covariates

Potential confounding variables were selected based on their relevance from prior literature. We used self-reported information collected during the follow-up period for these variables: age, race (white, black, other), household income (>$100,000/year), educational attainment (< high school, high school graduate, some college, college graduate or more), smoking status (never, former, current) and physical activity (engagement in regular exercise at least 20 minutes 3 times per week). Baseline rather than follow-up values were used for BMI and for perceived discrimination related to age, race, and/or sex (the three most common forms of discrimination (8)) because prolonged stress is more strongly related to allostatic load (28). These variables were computed in the same manner as weight discrimination.

Statistical Methods

Mixed linear models with maximum likelihood estimation and family membership as a random effect were used to examine the continuous associations between perceived weight discrimination and allostatic load. Family membership was incorporated as a random effect to account for clustering since the sample included participants from the sibling/twin subsamples of the main MIDUS study (31). A generalized linear model procedure was used to estimate relative risks (RR) using Poisson regression with robust error variance (41), as this method produces 95% confidence intervals with the correct coverage. Base models were adjusted for age and sex. The first multivariable adjusted model (Model 1) further adjusted for race, household income, smoking status, and educational attainment. Model 2 further incorporated physical activity, and

Model 3 was further adjusted for baseline perceived race, sex, and age discrimination. Our final model (Model 4) also adjusted for baseline BMI. We tested for the presence of interactions between perceived weight discrimination and sex, BMI, physical activity, smoking status, and race, sex, or age discrimination using a p-value<0.05 to establish significance. We also used Baron and Kenny criteria (42) to examine whether health behaviors like smoking and physical activity mediated the association between weight discrimination and allostatic load. Additionally, we examined the associations between perceived weight discrimination and individual system dysregulation in order to provide insight into the biological pathways underlying any observed associations. Finally, in sensitivity analyses, we excluded BMI and WHR from the definition of lipid/metabolic dysregulation in the calculation of allostatic load. All analyses were conducted with SAS v 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The study sample was predominately comprised of white (93%), female (57%), middle-aged adults (mean age=57y) with high educational attainment (47% with a college education or higher) (**Table 2**). More than 75% of participants reported engaging in regular physical activity, 15% were current smokers, and more than 75% were classified with either overweight or obesity. At baseline, nearly 4% of participants reported experiencing weight-related discrimination, with an average discrimination score of 0.13 (0.76). At follow-up, this percentage increased to approximately 6% with average discrimination values of 0.22 (1.09). When medication was included in the definition of high allostatic load, 18% of participants met the criteria, while only 13% met the criteria when medication usage was excluded.

No significant interactions between perceived weight discrimination and relevant covariates were detected (data not shown). Results were similar regardless of whether we used medications to operationalize allostatic load; thus, those presented hereafter include medication information to capture already-deregulated parameters. Compared to individuals who did not experience weight discrimination, both baseline and long-term perceived weight discrimination were associated with more than double the risk of high allostatic load in final multivariable models (RR: 2.07, 95%CI: 1.21, 3.55 for baseline discrimination and RR: 2.16, 95%CI: 1.39, 3.36 for long-term discrimination) (**Table 3**). Similar associations were observed when these associations were examined using the continuous weight discrimination score and allostatic load variables (β=0.11, p=0.01 for baseline discrimination and β=0. 19, p=0.0001 for long-term discrimination). Additionally, the effect of weight discrimination on allostatic load was partly mediated (~5%) through decreased physical activity among those who experienced versus did not experience weight discrimination (data not shown). Perceived race, sex, and age discrimination were not significantly associated with allostatic load in final models (data not shown). In sensitivity analyses, when BMI and WHR were excluded from the definition of allostatic load, baseline perceived weight discrimination was not significantly associated with allostatic load, but long-term weight discrimination remained associated with allostatic load after controlling for baseline BMI (RR:1.62, 95%CI: 1.01, 2.62; p=0.047).

Overall, compared to individuals reporting no weight-related discrimination, long-term weight discrimination was most strongly associated with metabolic/lipid dysregulation (RR: 1.56, 95%CI: 1.02, 2.40), glucose metabolism (RR:1.99, 95% CI: 1.34, 2.95), and inflammatory parameters (RR: 1.76. 95% CI: 1.22, 2.54) after adjustment for other confounding variables including baseline BMI (**Table 4**). Weight discrimination was not significantly associated with

287 CVD function, sympathetic or parasympathetic nervous system dysregulation, or HPA
288 dysfunction.
289
290 **DISCUSSION**
291 Perceived baseline and long-term weight discrimination were associated with more than
292 twice the risk of high allostatic load in this sample. The detrimental effects of weight
293 discrimination on allostatic load persisted following adjustment for BMI, suggesting that
294 perceived weight-related discrimination adversely affects overall physiological regulation
295 beyond what can be attributed to excess weight alone. Further support for the independent
296 associations between weight discrimination and allostatic load were observed when BMI and
297 WHR were excluded from the operationalization of allostatic load, and the long-term
298 associations remained significant. When the individual systems comprising allostatic load were
299 examined separately, perceived weight discrimination was most strongly associated with
300 lipid/metabolic dysregulation, glucose metabolism, and markers of inflammation. Taken
301 together, these results suggest that the stigma associated with having excess weight adversely
302 influences allostatic load, and potentially chronic disease morbidity and mortality, highlighting a
303 need for prevention efforts to reduce weight-related stigma in diverse settings.
304 While limited, empirical studies demonstrate that reducing weight-related stigma
305 favorably affects weight-loss self-efficacy and attitudes toward exercise. In an experimental
306 study, Pearl and Lebowitz (2014) demonstrated that overweight and obese participants who read
307 passages that implicate the food environment vs. personal responsibility in obesity etiology had
308 greater self-efficacy to lose weight and no increase in weight stigmatizing attitudes that
309 adversely affect weight control (5). Similarly, US women exposed to neutral vs. stereotypical

images of a woman with obesity exercising had more favorable attitudes toward exercise engagement and lower weight-based stigma (43).

Our results suggest that perceiving weight discrimination can adversely affect multiple biological systems and are consistent with research examining individual biomarkers. In MIDUS, Tsenkova and others (24) noted that experiencing weight discrimination amplified the adverse effects of elevated WHR on HbA1c. Among community-dwelling adults with diabetes, researchers found that participants experienced worse glycemic outcomes if they had experienced weight-based discrimination (11). Similar to the present study, the changes in glycemic markers persisted even after accounting for body weight and other forms of discrimination (11). Moreover, the participants from the study conducted by Potter and others also reported worse diabetes self-care practices related to diet, exercise, and blood glucose monitoring, providing insight into the pathways by which weight discrimination adversely impacts physiologic parameters. These observed negative behavioral adaptations support the pathways proposed in our conceptual model relating weight discrimination to allostatic load. Another study noted that weight-related discrimination was associated with inflammatory markers like CRP among overweight but not obese individuals (15), and also suggested that worse self-care practices may underlie the associations between weight-related discrimination and health outcomes. The significant findings in overweight rather than obese individuals implied that that weight discrimination may support the development and maintenance of obesity by activating inflammatory pathways (15).

Although allostatic load should primarily be evaluated as a matrix of dysregulated systems, investigating the individual systems informs our understanding of the biological underpinnings of an important risk marker. This study primarily implicated 3 of the 7 systems in

333 the association between weight discrimination and allostatic load, potentially identifying relevant
334 treatment priorities. However, additional research into all systems remains necessary because
335 the time course of metabolic dysregulation and the duration and mechanism of action of the
336 biomarkers is not well understood. For example, it remains unclear whether obesity precedes
337 HPA axis dysregulation or vice versa, and whether it results in hypo- or hyperactivity or
338 volatility (44). In the present study, many of the primary markers of HPA axis and CVD
339 dysregulation associated with allostatic load were not affected by perceived weight
340 discrimination, potentially suggesting that obesity precedes HPA axis dysregulation and induces
341 some volatility (44). However, because adrenal cortisol and adipose tissue cortisol may be
342 differentially affected by obesity (44) and because biomarkers were only measured once during
343 the follow-up period, we may have been unable to discern the critical window and/or site where
344 HPA dysregulation would occur.
345 Experiencing weight discrimination appears to promote many of the pathologic features
346 of obesity, such as inflammation, lipid/metabolic imbalances, glycemic dysregulation, and more
347 holistically, allostatic load. Although the pathways through which weight discrimination
348 influences allostatic load may be interconnected and multifactorial, this complexity provides
349 promising opportunities for further research. It may be informative to investigate how
350 discrimination relates to allostatic load parameters in more diverse populations where being
351 overweight is less stigmatized, and whether factors like healthcare access can also modulate the
352 effect of weight discrimination on health. While we did not detect any significant interactions
353 between perceived weight discrimination and physical activity or smoking, and detected minimal
354 mediation through physical activity, other research has found that health behaviors during
355 adulthood partly explain the association between adverse events in early life and subsequent

allostatic load (45). For example, research in MIDUS has established a link between positive coping strategies and social support on allostatic load (36) that warrants additional exploration in individuals who experience weight discrimination. Physical activity also deserves further attention as it is possible that a more precise measure would more strongly mediate the association between weight discrimination and allostatic load.

In addition, while the associations between weight discrimination and allostatic load were robust in this study, 10-years of follow-up may provide only an indication of the potential full effect that weight discrimination could have on cumulative physiological dysregulation throughout longer periods of time or at different lifecycles. More longitudinal research with longer follow-up periods and repeated measurements would enhance our understanding of the time course of weight discrimination related to allostatic load development as well as critical windows when risk can be modified (28). Finally, it may be important to establish confluence between clinical-cut points and population-based cut-points for the various biomarkers encompassing allostatic load to more accurately determine risk estimates.

Some limitations of the present analysis must be noted. Dietary information was not collected in the MIDUS study, which may be an important confounding or mediating variable in the association between perceived weight discrimination and allostatic load – particularly because poor dietary choices have been related to the effects of discrimination on glycemic control (46). Participant non-response rates on the questions about perceived discrimination also reduced the final sample size. Because non-response was higher among smoking, younger, women with lower self-reported physical activity, and higher BMI at baseline (data not shown), we expect that our risk estimates were attenuated and that the associations between weight discrimination and allostatic load are actually stronger than what we were able to observe.

379 Finally, because participants could select multiple primary reasons for discrimination, it is
380 possible that individuals who reported multiple forms of discrimination differed from individuals
381 who only reported weight discrimination. However, associations did not change after controlling
382 for other forms of reported discrimination, which improves the robustness of our findings.
383 The present study has several strengths that warrant mention. First, this study utilizes
384 data from a large US national sample. Additionally, much research to date examining allostatic
385 load have used limited markers or have been cross-sectional despite a call for more longitudinal
386 research (28); our study precisely measured multiple biomarkers across 7 systems, and the nearly
387 10 years of follow-up provide important insight into the cumulative effects of weight
388 discrimination as a stressor on multi-system dysregulation. By accounting for family
389 relationships within the cohort, we reduced bias related to shared genetic or environmental
390 factors that contribute to weight and metabolic dysregulation. The present study also builds upon
391 existing evidence that self-reported weight discrimination adversely influences biochemical
392 parameters beyond the effect of actual weight (11). Given the established connection between
393 personal responsibility campaigns and increased obesity stigma (5), the results from this study
394 have important policy implications with respect to framing obesity prevention campaigns as well
395 as treatment implications for clinicians working with clients with obesity.
396 The adverse health effects of obesity are well documented and require concerted efforts
397 to treat. The emphasis on personal responsibility in the US has had the effect of further
398 stigmatizing obesity, resulting in less favorable health outcomes within this vulnerable
399 population (4). Weight discrimination was recently associated with a nearly 60% increase in
400 overall mortality risk among MIDUS participants (47), and it is plausible that this hazard is at
401 least partly mediated by allostatic load. The magnitude of risk observed between weight

discrimination and allostatic load is greater than what has been observed for poor quality dietary patterns and allostatic load (40), and comparable to physical inactivity (48), drawing attention to weight discrimination as a significant allostatic load risk factor. Given that high allostatic load has been shown to be robustly associated with type 2 diabetes, hypertension, cardiovascular disease, and mortality (39, 49), targeted efforts to reduce weight discrimination are warranted. From a disease prevention standpoint, it is imperative to develop less stigmatizing public health campaigns and clinical approaches to reduce physiological dysregulation and long-term chronic disease risk among individuals with obesity or at risk for obesity. Simultaneously, directed efforts to better understand the pathways through which weight discrimination influences allostatic load can improve treatment targets and health outcomes among the substantial proportion of the population with weight-related comorbidities.

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Figure 1: Conceptual model of potential pathways through which obesity and weight discrimination are associated with allostatic load (Adapted from Gruenwald et al, 2012(31) and Tomiyama et al. 2014(3)

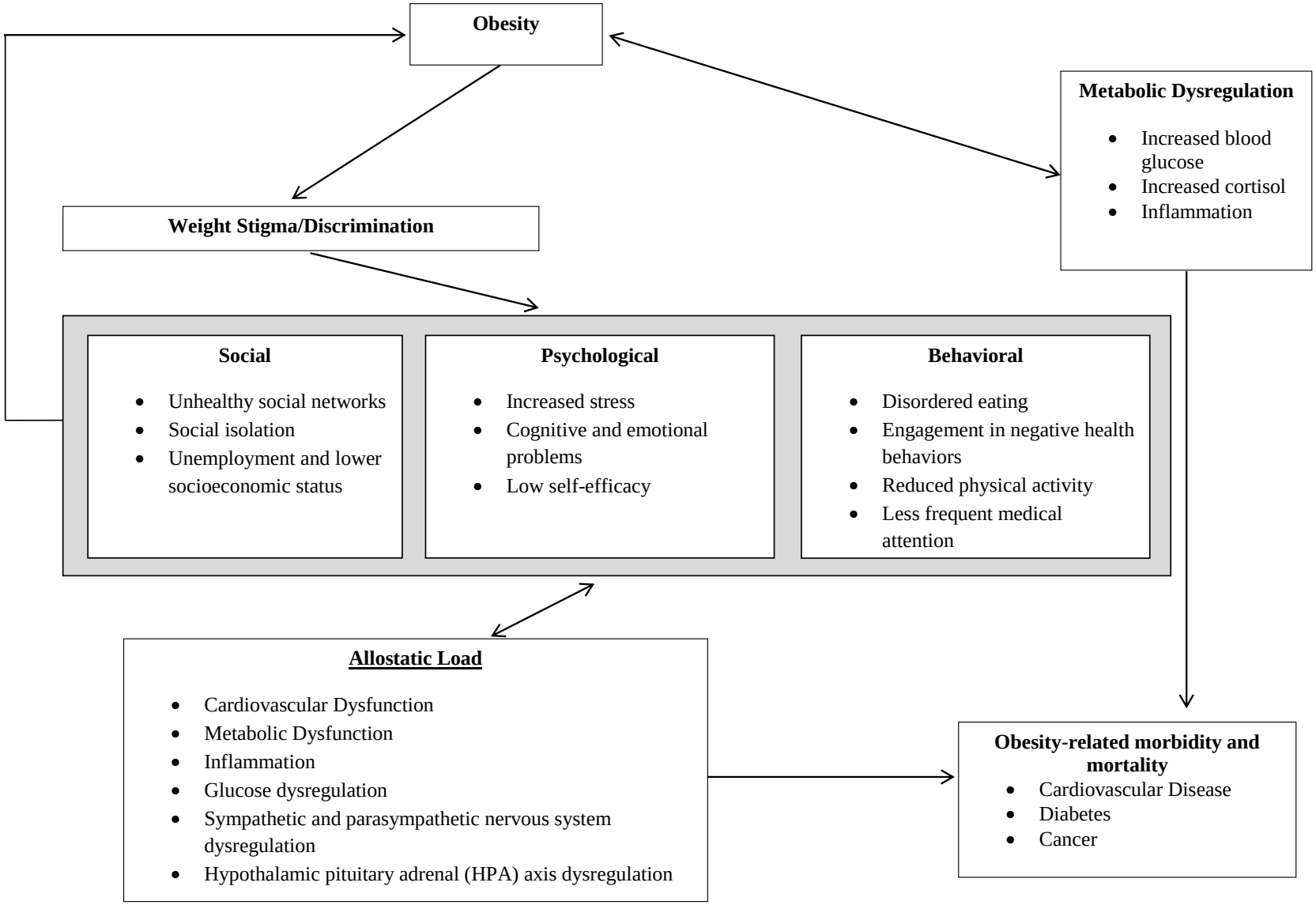

Table 1: Mean values and population-specific high-risk cutpoints for allostatic load parameters in the MIDUS Biomarker Substudy

System and Representative Biomarkers	N	Mean	SD	Min	Max	High-risk cutpoint by population-specific quartile
Cardiovascular						
Resting SBP (mmHg)	1254	131.5	18.3	83.0	222.0	≥144.0 (n=309)
Resting heart rate (bpm)	1253	71.1	11.2	36.0	111.0	≥79.0 (n=314)
Resting pulse pressure (mmHg)	1254	55.8	14.7	24.0	114.0	≥65.0 (n=312)
Metabolic- lipids						
BMI (kg/m^2)	1254	29.8	6.63	15.0	65.1	≥33.1 (n=313)
WHR	1253	0.89	0.10	0.62	1.72	≥0.97 (n=316)
Triglycerides (mg/dL)	1244	132.5	131.8	25.0	3299.0	≥156.0 (n=312)
HDL Cholesterol (mg/dL)	1242	55.4	18.0	19.0	121.0	≤42.0 (n=310)
LDL Cholesterol (mg/dL)	1242	105.5	35.4	6.00	283.0	≥128.0 (n=310)
Metabolic- glucose metabolism						
Glycosylated hemoglobin (%)	1235	6.10	1.16	3.58	19.7	≥6.24 (n=314)
Fasting glucose (mg/dL)	1236	102.1	28.4	5.00	418.0	≥105.0 (n=314)
Insulin resistance (HOMA-IR)	1236	3.58	3.98	0.04	53.7	≥4.36 (n=310)
Inflammation						
CRP (mg/L)	1235	3.02	4.78	0.14	61.7	≥3.66 (n=309)
IL6 (pg/mL)	1243	3.04	3.04	0.16	23.0	≥3.48 (n=310)
Fibrinogen (mg/dL)	1235	348.9	87.8	45.0	857.0	≥399.0 (n=313)
sE-Selectin (ng/MI)	1242	43.4	22.7	0.09	178.1	≥51.9 (n=310)
sICAM-1 (ng/MI)	1242	288.5	115.6	44.0	1076.6	≥335.8 (n=310)
Sympathetic Nervous System						
Urine Epinephrine (ug/g creatine)	1233	1.96	1.28	0.09	10.6	≥2.47 (n=308)
Urine Norepinephrine (ug/g creatine)	1243	27.4	13.9	3.50	187.1	≥33.0 (n=311)
Hypothalamic Pituitary Adrenal Axis						
Urine Cortisol (ug/g creatine)	1252	15.8	24.6	0.40	725.0	≥20.0 (n=308)
Blood DHEA-S (ug/dL)	1239	105.1	77.0	0.90	685.0	≤51.0 (n=313)
Parasympathetic Nervous System						
SDRR (msec)	1148	35.6	17.2	5.56	138.8	≤23.7 (n=287)

RMSSD	1148	22.9	17.7	2.64	209.7	≤12.1 (n=287)
Low frequency spectral power	1148	424.3	607.5	1.60	10943.6	≤114.6 (n=287)
High frequency spectral power	1148	316.5	729.4	2.45	15731.7	≤58.8 (n=287)
Allostatic Load	1233	1.72	1.03	0	5.03	
Allostatic Load (with medication data)	1233	1.94	1.10	0	5.37	

Abbreviations: BMI: body mass index; CRP: C-reactive protein; DHEA-S: dehydroepiandrosterone sulfate; PNS: parasympathetic nervous system; HPA: hypothalamic pituitary axis; IL6: interleukin-6; RMSSD: root mean square of successive differences; SBP: systolic blood pressure, SDRR: the standard deviation of R-R (heartbeat to heartbeat) intervals; sE-selectin: soluble adhesion molecule E-selectin; sICAM: soluble intracellular adhesion molecule-1; SNS: sympathetic nervous system

Allostatic Load was defined in accordance with previous studies conducted within this population using a score that captured dysregulation across seven systems, including multiple markers of cardiovascular pathways, Sympathetic Nervous System, Parasympathetic Nervous System, HPA axis, inflammation, lipid and general metabolic activity, and glucose metabolism, and could range from 0 to 7.

Table 2: Descriptive characteristics of the MIDUS participants at 10-year follow-up, (n=932-1,255)[a]

Age	57.3 (11.5)
Sex (% female)	56.8
Race	
White	93.1
Black	2.6
Other	4.4
Educational attainment (%)	
Less than high school	4.3
High school	19.9
Some college	29.2
College and above	46.6
Household income (>$100,000/year)	21.4
Regular physical activity (%)[b]	76.5
Smoking status (%)	
Never	52.4
Past	32.6
Current	14.9
Body Mass Index	29.8 (6.6)
Weight category (%)	
Overweight	35.1
Obesity	41.2
Perceived weight discrimination (%) [c]	
Baseline	3.96
10-year follow-up	6.17
Perceived weight discrimination score [c]	
Baseline	0.13 (0.76)
10-year follow-up	0.22 (1.09)
High allostatic load[d]	18.3
High allostatic load (excluding medication)[d]	12.9

[a]Continuous variables are expressed as mean (SD) and categorical variables as percentages

[b]Physical activity was defined as the percentage who regularly exercised at least 20 min 3 times per week.

[c]Perceived weight discrimination measured how often participants experienced discrimination due to their weight in nine situations on a daily basis. For the categorical measure, anyone who reported any weight discrimination ("often" or "sometimes") was counted. For the continuous score measure, we summed the number of instances a person reported discrimination "sometimes" (assigned as 1 point) or "often" (assigned as 2 points). Individuals who reported discrimination "never" or "rarely" received a score of 0. Baseline values were carried forward for individuals who reported weight discrimination at baseline, but had missing data at follow-up.

[d]High allostatic load was defined as greater than or equal to 3 dysregulated systems and low allostatic load was defined as less than 3. Allostatic load was measured at follow-up.

Table 3: Relative Risk of High Allostatic Load based on Perceived Baseline and Long-Term Weight Discrimination in the MIDUS Study

	High Allostatic Load[a]			Continuous Allostatic Load[b]			High Allostatic Load (excluding BMI and WHR)		
	RR	**95% CI**	**p-value**	**β**	**SE**	**p-value**	**RR**	**95% CI**	**p-value**
Baseline perceived weight discrimination[c]									
Age- and sex-adjusted	2.60	1.60, 4.23	0.0001	0.15	0.04	0.0005	1.92	1.14, 3.23	0.01
Multivariable-adjusted Model 1[d]	2.42	1.44, 4.04	0.0008	0.14	0.04	0.001	1.78	1.02, 3.11	0.04
Multivariable-adjusted Model 2[e]	2.31	1.38, 3.84	0.001	0.13	0.04	0.002	1.71	0.99, 2.97	0.05
Multivariable-adjusted Model 3[f]	2.23	1.28, 3.87	0.004	0.13	0.04	0.005	1.61	0.90, 2.87	0.11
Multivariable-adjusted Model 4[g]	2.07	1.21, 3.55	0.008	0.11	0.04	0.01	1.55	0.87, 2.75	0.13
Long-term perceived weight discrimination[c,h]									
Age- and sex-adjusted	2.50	1.72, 3.63	<0.0001	0.21	0.04	<0.0001	1.87	1.25, 2.79	0.002
Multivariable-adjusted Model 1[d]	2.47	1.65, 3.69	<0.0001	0.21	0.04	<0.0001	1.79	1.15, 2.78	0.01
Multivariable-adjusted Model 2[e]	2.37	1.58, 3.56	<0.0001	0.20	0.04	<0.0001	1.73	1.11, 2.69	0.02
Multivariable-adjusted Model 3[f]	2.27	1.45, 3.56	0.0003	0.21	0.05	<0.0001	1.66	1.03, 2.69	0.04
Multivariable-adjusted Model 4[g]	2.16	1.39, 3.36	0.0007	0.19	0.05	0.0001	1.62	1.01, 2.62	0.047

[a]High allostatic load was defined as greater than or equal to 3 dysregulated systems, and low allostatic load was defined as less than 3. Allostatic load was measured at follow-up, and medication usage was included in the definition.

[b]Family status was added to the continuous models as a random effect.

[c]Only individuals who reported discrimination "sometimes" or "often" were coded as having experienced discrimination.

[d]Model 1 includes age, sex, race (white, black, other), household income (>$100,000/year), smoking status (never, former, current), educational attainment (< high school, high school graduate, some college, college graduate or more)

[e]Model 2 includes covariates in Model 1 plus engagement in regular exercise at least 20 min 3 times per week

[f]Model 3 includes covariates in Models 1-2 plus perceived race, sex, and age discrimination at baseline

[g]Model 4 includes covariates in Models 1-3 plus baseline BMI

[h]Long-term weight discrimination was computed as the average value of perceived discrimination at baseline and at 10-year follow-up for those who had both measures. For individuals with no baseline measure, but with a measure at 10-years, long-term discrimination was computed as their reported discrimination at 10-years.

635 **Table 4:** Relative Risk of High Allostatic Load System Parameters based on Perceived Long-Term Weight
636 Discrimination in the MIDUS Study[a]

	Percent with dysregulated system	RR	95% CI	p-value
Cardiovascular	38.6			
Age and sex-adjusted		1.37	1.03, 1.81	0.03
Model1[b]		1.26	0.92, 1.72	0.15
Model 2[c]		1.20	0.89, 1.65	0.23
Model 3[d]		1.24	0.89, 1.72	0.20
Model 4[e]		1.23	0.89, 1.72	0.21
Metabolic	18.3			
Age and sex-adjusted		2.07	1.49, 2.88	<0.0001
Model 1[b]		2.07	1.45, 2.97	<0.0001
Model 2[c]		1.96	1.35, 2.82	0.0003
Model 3[d]		1.66	1.07, 2.57	0.02
Model 4[e]		1.56	1.02, 2.40	0.04
Glucose Metabolism	23.5			
Age and sex-adjusted		2.29	1.62, 3.24	<0.0001
Model 1[b]		2.29	1.43, 3.67	0.0006
Model 2[c]		2.26	1.59, 3.22	<0.0001
Model 3[d]		2.10	1.40, 3.15	0.0003
Model 4[e]		1.99	1.34, 2.95	0.0006
Inflammation	26.6			
Age and sex-adjusted		1.89	1.37, 2.61	<0.0001
Model 1[b]		1.99	1.44, 2.76	<0.0001
Model 2[c]		1.91	1.37, 2.67	0.0001
Model 3[d]		1.83	1.27, 2.64	0.001
Model 4[e]		1.76	1.22, 2.54	0.003
Sympathetic Nervous System[f]	12.4			
Age and sex-adjusted		1.27	0.70, 2.32	0.43
Model 1[b]		1.26	0.67, 2.35	0.47
Model 2[c]		1.24	0.66, 2.32	0.50

Model 3[d]		1.31	0.64, 2.68	0.46
Model 4[e]		1.44	0.70, 2.96	0.32
Hypothalamic Pituitary Axis	43.6			
Age and sex-adjusted		0.94	0.71, 1.24	0.66
Model 1[b]		0.96	0.71, 1.28	0.77
Model 2[c]		0.97	0.72, 1.30	0.84
Model 3[d]		0.94	0.69, 1.30	0.72
Model 4[e]		0.95	0.69, 1.31	0.77
Parasympathetic Nervous System[f]	19.6			
Age and sex-adjusted		1.42	0.90, 2.23	0.13
Model 1[b]		1.42	0.86, 2.33	0.17
Model 2[c]		1.38	0.83, 2.29	0.21
Model 3[d]		1.28	0.75, 2.21	0.36
Model 4[e]		1.29	0.75, 2.21	0.37

[a]Long-term perceived weight discrimination represents the average value of perceived discrimination at baseline and at follow-up for those who had both measures. For individuals with only one measure, long-term discrimination represents their reported discrimination at that time point

[b]Model 1 includes age, sex, race (white, black, other), household income (>$100,000/year), smoking status (never, former, current), educational attainment (< high school, high school graduate, some college, college graduate or more)

[c]Model 2 includes covariates in Model 1 plus engagement in regular exercise at least 20 min 3 times per week

[d]Model 3 includes covariates in Models 1-2 plus perceived race, sex, and age discrimination at baseline

[e]Model 4 includes covariates in Models 1-3 plus baseline BMI

[f]Medication usage was not considered in the diagnosis of Parasympathetic Nervous System or Sympathetic Nervous System dysregulation.