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

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

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28 **ABSTRACT**

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

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

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

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

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

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

54  
55 **Word Count:** 250  
56

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

59

60 **INTRODUCTION**

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

68 Research suggests that pervasive individually-targeted health campaigns increase public  
69 prejudice toward individuals with obesity by increasing the perception of obesity as a lifestyle  
70 choice resulting from weakness of character (5). A downward consequence of this perception is  
71 increased weight-related stigma, and often, discrimination (6, 7). Weight discrimination is the  
72 fourth most prevalent form of discrimination among adults, after age, sex, and race-based  
73 discrimination (8). Between 1995 and 2006, the absolute prevalence of weight discrimination  
74 increased from 7% to 12% in the US, representing a 66% increase in prevalence and exceeding  
75 the proportion that could be attributed to concomitant increases in obesity (9). Despite the lay  
76 belief that weight stigma motivates positive behavioral change (10), most evidence demonstrates  
77 that weight shaming promotes poorer dietary and exercise practices and health care avoidance  
78 (11, 12), akin to how experienced racism correlates with negative health outcomes like cancer  
79 risk (13, 14). As such, weight discrimination may contribute to obesity (3, 15) by discouraging  
80 individuals from seeking treatment, reducing engagement with social support, or promoting  
81 disordered eating patterns, less healthful food choices, and emotional dysregulation (12, 16-21).  
82 Furthermore, weight stigma has been directly linked to overeating and physical inactivity in

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

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

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

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

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

113

## 114 **METHODS**

### 115 *Participants*

116 We used data from the MIDUS I (1995-1996), MIDUS II (2004-2006), and MIDUS  
117 Biomarker Substudy (2004-2009) to examine associations between perceived weight  
118 discrimination, **allostatic load**, and the individual systems comprising **allostatic load**. Detailed  
119 information about the study's sampling procedures have been previously published (33). Briefly,  
120 7,108 non-institutionalized adults (including 950 siblings and 1,914 twins) aged 25-74y  
121 participated in a telephone survey conducted via random digit dialing in 1995-1996. At follow-  
122 up between 9 and 10 years later, approximately 4,900 members of the original cohort responded  
123 to an additional phone survey; the mortality-adjusted longitudinal response rate at MIDUS II was  
124 75%. During the 10-year follow-up, a subset of 1,255 adults who completed the phone interview  
125 and questionnaires were randomly selected and invited to participate in a biomarker substudy.  
126 The present analysis includes those in the biomarker sub-study with sufficient information to  
127 compute **allostatic load** (n=1,233) or the individual **allostatic load** systems (n=1,158-1,254) and  
128 who had information on perceived weight discrimination (n=986).

129 *Perceived Weight Discrimination*

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

141 **Similar to Puhl and others (8), only participants reporting discrimination ‘Sometimes’ or**  
142 **‘Often’ were counted as instances of discrimination.** We constructed a continuous measure of  
143 perceived discrimination that allocated 2 points for every instance that a discrimination scenario  
144 was reported as ‘Often’, 1 point for every scenario reported as ‘Sometimes’, and 0 points for  
145 those who reported discrimination ‘Rarely’ or ‘Never’. Separately, participants were asked to  
146 select the primary reason(s) for discrimination, from among the following options: age, gender,  
147 race, height or weight, ethnicity or nationality, physical disability, some aspect of appearance  
148 other than weight or height, sexual orientation, religion, and other reason. Like previous studies,  
149 we refer to the ‘height or weight’ variable as ‘weight discrimination’ throughout the manuscript  
150 (8).



151 We constructed two variables for perceived weight discrimination at both baseline and  
152 10-year follow-up. First, a continuous measure of perceived weight discrimination was  
153 computed from the continuous perceived discrimination score for individuals who reported  
154 ‘weight’ as a primary reason for discrimination. The observed range for this score was 0-10 at  
155 baseline and 10-year follow-up. Secondly, a categorical indicator variable was created for  
156 individuals who experienced any vs. no perceived weight discrimination.

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

### 167 *Allostatic Load*

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

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

175 **Sympathetic nervous system** functioning was measured with 12-hour overnight urinary  
176 measurements of epinephrine and norepinephrine via high-pressure liquid chromatography, and  
177 levels were reported per level of creatinine (g). **Parasympathetic nervous system** activity was  
178 measured by four heart rate variability parameters during an 11-minute seated rest period using  
179 an electrocardiograph: low frequency spectral power, high frequency spectral power, the  
180 **standard deviation of heartbeat to heartbeat intervals**, and the **root mean square of successive**  
181 **differences**. Overnight urinary cortisol and serum dehydroepiandrosterone sulfate (DHEA-S)  
182 were used as markers of HPA activity. Markers of cardiovascular functioning included resting  
183 systolic blood pressure (SBP), heart rate, and pulse pressure. Lipid/fat metabolism markers  
184 included high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, body  
185 mass index (BMI), and waist-to-hip ratio (WHR). Glycosylated hemoglobin (HbA1c), fasting  
186 glucose, and the homeostasis model of insulin resistance (HOMA-IR) were used to assess  
187 glucose metabolism. Inflammation was measured with plasma **CRP**, fibrinogen, serum  
188 interleukin-6 (IL6), the soluble adhesion molecule E-selectin, and intracellular adhesion  
189 molecule-1. All blood, urine, saliva, cardiovascular, and heart rate variability measurements were  
190 collected during an overnight stay at one of three University General Clinical Research **Centers**.  
191 Detailed collection protocols for each biomarker have been previously published (31, 37).  
192 Consistent with previous studies (36), we computed a system risk score for each of the seven  
193 systems that was in the upper or lower quartile of the biomarker population-specific distribution,  
194 based on whether high or low values of the parameter were generally associated with higher  
195 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

219 low **allostatic load** was created: **allostatic load** summary scores  $\geq 3$  were considered “high” and  
220 scores  $< 3$  were considered “low.” Although the median **allostatic load** score in this population  
221 was 2, using a higher cut-point allowed us to capture individuals at higher disease risk (39).

## 222 *Covariates*

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

## 232 *Statistical Methods*

233 Mixed linear models with maximum likelihood estimation and family membership as a  
234 random effect were used to examine the continuous associations between perceived weight  
235 discrimination and **allostatic load**. Family membership was incorporated as a random effect to  
236 account for clustering since the sample included participants from the sibling/twin subsamples of  
237 the main MIDUS study (31). A generalized linear model procedure was used to estimate relative  
238 risks (RR) using Poisson regression with robust error variance (41), as this method produces  
239 95% confidence intervals with the correct coverage. Base models were adjusted for age and sex.  
240 The first multivariable adjusted model (Model 1) further adjusted for race, household income,  
241 smoking status, and educational attainment. Model 2 further incorporated physical activity, and

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

253

## 254 **RESULTS**

255 The study sample was predominately comprised of white (93%), female (57%), middle-  
256 aged adults (mean age=57y) with high educational attainment (47% with a college education or  
257 higher) (**Table 2**). More than 75% of participants reported engaging in regular physical activity,  
258 15% were current smokers, and more than 75% were classified with either overweight or obesity.  
259 At baseline, nearly 4% of participants reported experiencing weight-related discrimination, with  
260 an average discrimination score of 0.13 (0.76). At follow-up, this percentage increased to  
261 approximately 6% with average discrimination values of 0.22 (1.09). When medication was  
262 included in the definition of high **allostatic load**, 18% of participants met the criteria, while only  
263 13% met the criteria when medication usage was excluded.

264 No significant interactions between perceived weight discrimination and relevant  
265 covariates were detected (data not shown). Results were similar regardless of whether we used  
266 medications to operationalize **allostatic load**; thus, those presented hereafter include medication  
267 information to capture already-deregulated parameters. Compared to individuals who did not  
268 experience weight discrimination, both baseline and long-term perceived weight discrimination  
269 were associated with more than double the risk of high **allostatic load** in final multivariable  
270 models (RR: 2.07, 95%CI: 1.21, 3.55 for baseline discrimination and RR: 2.16, 95%CI: 1.39,  
271 3.36 for long-term discrimination) (**Table 3**). Similar associations were observed when these  
272 associations were examined using the continuous weight discrimination score and **allostatic load**  
273 variables ( $\beta=0.11$ ,  $p=0.01$  for baseline discrimination and  $\beta=0.19$ ,  $p=0.0001$  for long-term  
274 discrimination). Additionally, the effect of weight discrimination on **allostatic load** was partly  
275 mediated (~5%) through decreased physical activity among those who experienced versus did  
276 not experience weight discrimination (data not shown). Perceived race, sex, and age  
277 discrimination were not significantly associated with **allostatic load** in final models (data not  
278 shown). In sensitivity analyses, when BMI and WHR were excluded from the definition of  
279 **allostatic load**, baseline perceived weight discrimination was not significantly associated with  
280 **allostatic load**, but long-term weight discrimination remained associated with **allostatic load** after  
281 controlling for baseline BMI (RR:1.62, 95%CI: 1.01, 2.62;  $p=0.047$ ).

282 Overall, compared to individuals reporting no weight-related discrimination, long-term  
283 weight discrimination was most strongly associated with metabolic/lipid dysregulation (RR:  
284 1.56, 95%CI: 1.02, 2.40), glucose metabolism (RR:1.99, 95% CI: 1.34, 2.95), and inflammatory  
285 parameters (RR: 1.76. 95% CI: 1.22, 2.54) after adjustment for other confounding variables  
286 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

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

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

330 Although **allostatic load** should primarily be evaluated as a matrix of dysregulated  
331 systems, investigating the individual systems informs our understanding of the biological  
332 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

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

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

370 Some limitations of the present analysis must be noted. Dietary information was not  
371 collected in the MIDUS study, which may be an important confounding or mediating variable in  
372 the association between perceived weight discrimination and **allostatic load** – particularly  
373 because poor dietary choices have been related to the effects of discrimination on glycemic  
374 control (46). Participant non-response rates on the questions about perceived discrimination also  
375 reduced the final sample size. Because non-response was higher among smoking, younger,  
376 women with lower self-reported physical activity, and higher BMI at baseline (data not shown),  
377 we expect that our risk estimates were attenuated and that the associations between weight  
378 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

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

413

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415

416

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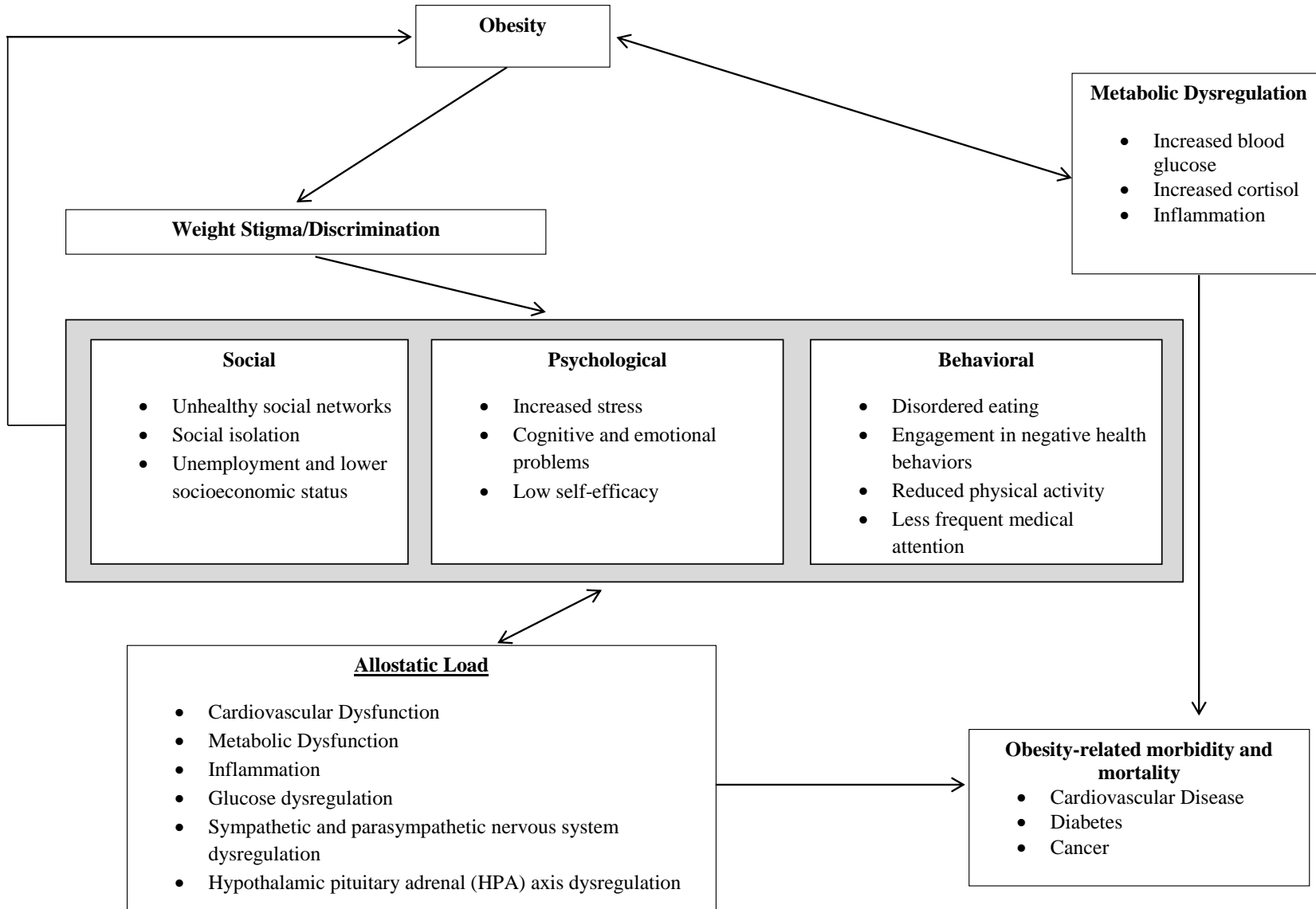
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591 **Figure 1:** Conceptual model of potential pathways through which obesity and weight discrimination are associated with allostatic load  
 592 (Adapted from Gruenwald et al, 2012(31) and Tomiyama et al. 2014(3))  
 593



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

| <b>System and Representative Biomarkers</b> | <b>N</b> | <b>Mean</b> | <b>SD</b> | <b>Min</b> | <b>Max</b> | <b>High-risk cutpoint by population-specific quartile</b> |
|---|----------|-------------|-----------|------------|------------|---|
| <i>Cardiovascular</i>                       |          |             |           |            |            |   |
| 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)   |
| <i>Metabolic- lipids</i>                    |          |             |           |            |            |   |
| BMI (kg/m <sup>2</sup> )                    | 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)  |
| <i>Metabolic- glucose metabolism</i>        |          |             |           |            |            |   |
| 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)   |
| <i>Inflammation</i>                         |          |             |           |            |            |   |
| 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)  |
| <i>Sympathetic Nervous System</i>           |          |             |           |            |            |   |
| 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)   |
| <i>Hypothalamic Pituitary Adrenal Axis</i>  |          |             |           |            |            |   |
| 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)   |
| <i>Parasympathetic Nervous System</i>       |          |             |           |            |            |   |
| 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)  |
|  | <i>Allostatic Load</i>                        | 1233 | 1.72  | 1.03  | 0    | 5.03    |                |
|  | <i>Allostatic Load (with medication data)</i> | 1233 | 1.94  | 1.10  | 0    | 5.37    |                |

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

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

605

606

607 **Table 2:** Descriptive characteristics of the MIDUS participants at 10-year follow-up, (n=932-1,255)<sup>a</sup>

|  |                       |             |
|--|-----------------------|-------------|
| 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 (%) <sup>b</sup>               |                       | 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 (%) <sup>c</sup>         |                       |             |
|  | Baseline              | 3.96        |
|  | 10-year follow-up     | 6.17        |
| Perceived weight discrimination score <sup>c</sup>       |                       |             |
|  | Baseline              | 0.13 (0.76) |
|  | 10-year follow-up     | 0.22 (1.09) |
| High allostatic load <sup>d</sup>                        |                       | 18.3        |
| High allostatic load (excluding medication) <sup>d</sup> |                       | 12.9        |

608 <sup>a</sup>Continuous variables are expressed as mean (SD) and categorical variables as percentages

609 <sup>b</sup>Physical activity was defined as the percentage who regularly exercised at least 20 min 3 times per week.

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

616 <sup>d</sup>High allostatic load was defined as greater than or equal to 3 dysregulated systems and low allostatic load was  
 617 defined as less than 3. Allostatic load was measured at follow-up.

618

619

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

|  | High Allostatic Load <sup>a</sup> |            |         | Continuous Allostatic Load <sup>b</sup> |      |         | High Allostatic Load (excluding BMI and WHR) |            |         |
|--|-----------------------------------|------------|---------|---|------|---------|--|------------|---------|
|  | RR                                | 95% CI     | p-value | $\beta$                                 | SE   | p-value | RR   | 95% CI     | p-value |
| <b>Baseline perceived weight discrimination<sup>c</sup></b>    |                                   |            |         |   |      |         |  |            |         |
| 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 <sup>d</sup>                    | 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 <sup>e</sup>                    | 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 <sup>f</sup>                    | 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 <sup>g</sup>                    | 2.07                              | 1.21, 3.55 | 0.008   | 0.11                                    | 0.04 | 0.01    | 1.55   | 0.87, 2.75 | 0.13    |
| <b>Long-term perceived weight discrimination<sup>c,h</sup></b> |                                   |            |         |   |      |         |  |            |         |
| 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 <sup>d</sup>                    | 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 <sup>e</sup>                    | 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 <sup>f</sup>                    | 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 <sup>g</sup>                    | 2.16                              | 1.39, 3.36 | 0.0007  | 0.19                                    | 0.05 | 0.0001  | 1.62   | 1.01, 2.62 | 0.047   |

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

624 <sup>b</sup>Family status was added to the continuous models as a random effect.

625 <sup>c</sup>Only individuals who reported discrimination “sometimes” or “often” were coded as having experienced discrimination.

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

628 <sup>e</sup>Model 2 includes covariates in Model 1 plus engagement in regular exercise at least 20 min 3 times per week

629 <sup>f</sup>Model 3 includes covariates in Models 1-2 plus perceived race, sex, and age discrimination at baseline

630 <sup>g</sup>Model 4 includes covariates in Models 1-3 plus baseline BMI

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

634

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

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

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

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

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

643 <sup>c</sup>Model 2 includes covariates in Model 1 plus engagement in regular exercise at least 20 min 3 times per week

644 <sup>d</sup>Model 3 includes covariates in Models 1-2 plus perceived race, sex, and age discrimination at baseline

645 <sup>e</sup>Model 4 includes covariates in Models 1-3 plus baseline BMI

646 <sup>f</sup>Medication usage was not considered in the diagnosis of **Parasympathetic Nervous System** or **Sympathetic Nervous System**  
647 dysregulation.

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