Effects of Acetaminophen on Pain Response among Overweight or Obese Women Exposed to Weight Stigmatization

RESEARCH PROTOCOL

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Chapter 1: Introduction

Pain is widely prevalent, with recent estimates suggesting that approximately 50 million U.S. adults and 30-50% of the world population suffer from chronic pain (Barcellos de Souza et al., 2017; Dahlhamer et al., 2018). Recent analysis of a 2012 U.S. National Health Interview Survey revealed that an estimated 126 million American adults experienced pain during the prior three months (Nahin, 2015). Pain may be secondary to several chronic conditions and diseases (e.g., cancer-related pain, chronic neuropathic pain), but, in some cases, chronic pain may be considered a disease itself (e.g., low back pain, fibromyalgia; Treede et al., 2019). Chronic pain is associated with several negative outcomes such as restrictions in mobility and daily activities, anxiety, depression, poor perceived health, reduced quality of life, and increased risk for dependence on opioids (Dahlhamer et al., 2018).

Pain is a subjective experience that involves both physiological and psychological processes. Experiences of pain, in turn, influence reactions to new episodes of pain. From an evolutionary perspective, learning from previous pain experiences may help individuals avoid potentially dangerous objects in their environment, cope with new pain more effectively, and maintain good health (Linton & Shaw, 2011). For these reasons, the psychological processes involved in pain hold value for human survival. Thus, eliminating pain from the human experience is not an adaptive clinical goal. However, pain that is insufficiently managed, such as chronic pain, may contribute to unnecessary or exacerbated suffering. Therefore, there is increased need to develop more effective interventions for pain management (Tompkins, Hobelmann, & Compton, 2017).

Chronic pain is positively associated with body weight such that individuals with overweight and obesity are disproportionately affected by pain relative to individuals with

normal weight (Okifuji & Hare, 2015). Indeed, results from a recent multi-state study revealed that pain complaints were more common as body mass index (BMI) increased, and that individuals with obesity are four times more likely to complain about pain compared to individuals without obesity (Hitt, McMillen, Thornton-Neaves, Koch, & Cosby, 2007). While efficacious pain management interventions may be utilized to help individuals cope with chronic pain, recent evidence suggests that these may not always be as effective for individuals with higher BMI. For example, Sellinger and colleagues (2010) found that individuals with obesity were less likely than individuals without obesity to benefit from a cognitive behavioral treatment for low back pain. Thus, obesity is associated with exacerbated pain, and may complicate the treatment of pain.

Obesity

Obesity is a chronic medical condition of excessive or abnormal fat accumulation in adipose tissue (Garrow, 1981) commonly defined using BMI, which is an approximation of percentage body fat using the ratio of one's body weight (in kilograms) to height (in meters squared). A BMI of 30 or greater is classified as obese (U.S. National Library of Medicine, 2015). There is growing public health concern regarding obesity; 2014 estimates from the World Health Organization revealed that 39% of adults worldwide were classified as overweight (BMI ≥ 25 and < 30), while 13% of adults met criteria for obesity. The prevalence of obesity in the United States is rising at an even more alarming rate. A recent, population-based study of 9,000 adults found that 34% of the sample was overweight, and an additional 35% met criteria for obesity (Ogden, Carrol, Kit, & Flegal, 2014). Increased prevalence of obesity contributed to higher average medical costs, estimated at $1,000 more per year than costs for individuals with

normal weight (Finkelstein, Trogdon, Cohen, & Dietz, 2009), in addition to increased risk of physical problems such as pain.

Physical Pain and Obesity

Several studies have investigated the relationship of obesity with specific forms of chronic pain. Studies have documented links between obesity and a variety of pain diagnoses including low back pain and abdominal pain (Wright et al., 2010). A 2014 review by Chai and colleagues revealed that individuals with obesity are at greater risk for experiencing headaches, especially chronic headaches. Other research reveals that obesity may be a risk factor for pelvic and neuropathic pains (Okifuji & Hare, 2015). Studies among individuals with pain conditions provide support for the connection between pain and obesity. For example, in studies of patients with fibromyalgia, a significant proportion is overweight or obese (Okifuji, Bradshaw, & Olson, 2009; Okifuji, Donaldson, Barck, & Fine, 2010; Yunus, Arslan, & Aldag, 2002). Yoo and colleagues (2014) found greater total fat mass and less total lean mass among individuals reporting musculoskeletal pain than among those not reporting pain.

The relationship between obesity and pain may be bidirectional such that obesity not only contributes to pain, but also is a product of pain. Several longitudinal studies have revealed greater risk for pain among individuals with obesity. For example, Mork, Holtermann, and Nilsen (2013) followed over 30,000 people in Norway for over ten years and found that those with obesity, especially those who were inactive, were more likely to develop chronic arm pain. Other, larger longitudinal studies have found that obesity is a risk factor for future multisite musculoskeletal pain (e.g., low back, neck, knees; Haukka, Ojajarvi, Takala, Viikari-Juntura, & Leino-Arjas, 2012; Heuch, Heuch, Hagen, & Zwart, 2013). In support of obesity as a product of pain, common effects of chronic pain such as poor sleep and sedentary lifestyle are linked to

weight gain among chronic pain patients (Okifuji & Hare, 2015). Individuals treated for chronic pain via medication may experience unpleasant side-effects that can contribute to weight gain such as mood changes, difficulty sleeping, and opioid-induced androgen deficiency. A study of self-reported causes of weight gain among pre-bariatric surgery patients highlighted chronic pain as one of the major reasons patients believed they had developed obesity (Ferguson et al., 2013). While weight loss may attenuate pain, pain also may interfere with successful weight loss in ways such as limiting one's ability to engage in physical activity (Masheb et al., 2015).

Several mechanisms have been postulated to help explain the relationship between obesity and pain, including structural and biochemical factors, as well as metabolic and inflammatory processes.

Structural and Mechanical Factors

Obesity is thought to contribute to chronic pain via negative effects of greater weight on joints and the spine. In support of this link, prior research has documented a positive relationship between BMI and defective change in knee cartilage which, in turn, may produce pain (Ding, Cicuttini, Scott, Cooley, & Jones, 2005). Individuals with obesity also produce greater spinal disk compression force when lifting objects than do individuals with normal weight, which may help explain the relation of obesity to greater structural damage in the back (Okifuji & Hare, 2015; Singh, Park, Hwang, & Levy, 2014). Changes in body posture also are potentially implicated in the relationship between pain and obesity as they are common among individuals with obesity (Fabris de Souza et al., 2005). Structural abnormalities of the spine may lead to poor ambulation, and by extension muscular deconditioning (Narouze & Souzdalnitski, 2015). In fact, obesity in combination with low back pain may negatively affect gait more than obesity alone (Cimonlin et al., 2011).

Metabolic and Inflammatory Mechanisms

Adipose tissue is metabolically active and, like other endocrine organs in the body, produces and releases adipokines and proinflammatory cytokines. It has been suggested that these endocrine changes may act as chemical mediators in the relationship between obesity and pain (Okifuji & Hare, 2015; Ronti, Lupattelli, & Mannarino, 2006). Indeed, prior studies have found that obesity is associated with elevated levels of inflammatory markers such as interleukin-6 (IL-6), interleukin-1 (IL-1), C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-α), as well as elevated levels of macrophages which are known to be associated with inflammation (Wellen & Hotamisligil, 2003). These data are consistent with the assertion that obesity is associated with chronic low-grade inflammation, which may in turn contribute to pain. High concentrations of CRP have been found to increase odds of experiencing low back pain, especially among individuals with obesity (Briggs, Givens, Schmitt, & Taylor, 2013). In addition, obesity is associated with greater potential for experiencing migraines, and inflammatory factors appear to be a mechanism (Bigal & Rapaport, 2012). Achieving weight loss through activities such as aerobic exercise may help individuals better cope with migraine via reduction of inflammatory markers that are associated with both obesity and migraine (Bigal & Lipton, 2006; Bigal & Rapaport, 2012). In fact, a recent study of women with obesity and chronic migraines who received bariatric surgery found that headache frequency and impairment from headaches decreased in the months following surgery, and that reduced inflammation may have contributed to the change (Novak et al., 2011).

Many studies of obesity have focused on the role of leptin, a hormone that is both synthesized and secreted primarily by adipocytes. Obesity is associated with higher leptin levels (Considine, 2005). The primary role of leptin is to signal energy intake and energy stores in the

body to the central nervous system, allowing the hypothalamus to help maintain stable body weight. Elevated leptin levels have been found in individuals with obesity and osteoarthritis; and leptin appeared to contribute to additional inflammation and general joint damage, both of which may exacerbate pain (Vuolteenaho, Koskinen, & Moilanen, 2014).

Dietary factors are associated with both inflammatory markers and leptin. Excessive food consumption, especially excessive consumption of saturated fatty acids, is associated with growth of adipose tissue, greater low-grade systemic inflammation, and leptin resistance. As a result, concentrations of leptin may increase, triggering inflammation and, by extension, promotion of joint damage that contributes to the experience of pain (Narouze & Souzdalnitski, 2015; Penninx et al., 2004).

Other hormone-like substances of relevance for obesity are the prostaglandins, a type of eicosanoid, or acid metabolite, formed through cyclooxegenase (COX) or a lipoxygenase metabolic pathway. Prostaglandins perform a variety of functions including, but not limited to, mediating the inflammatory response and regulating the lipolysis of adipose tissue. Research has shown that biosynthesis of prostaglandins is increased in acutely inflamed tissue (Ricciotti & FitzGerald, 2011), and that obesity is associated with overproduction of prostaglandins, thereby interfering with lipolysis of adipose tissue (Curtis-Prior, 1975). High levels of pro-inflammatory prostaglandins and cytokines have been observed in bones and joints that are overloaded due to elevated body weight (McVinnie, 2013). Thus, excess prostaglandin production may be evident in the adipose tissue growth and elevated inflammation characteristic of obesity.

Prostaglandin E2 (PGE_2) is of particular interest because it is a lipid mediator produced by the activity of COX that contributes to inflammatory pain and may have a significant impact on the processing of pain signals (Kawabata, 2011). Research has demonstrated that anti-

inflammatory drugs inhibiting COX, such as ibuprofen and acetaminophen, are effective in reducing the production of prostaglandins such as PGE_2. Reduced production of PGE_2 is associated with diminished inflammatory pain in various groups of patients with chronic pain, including rheumatoid arthritis, osteoarthritis, and migraine (Kawabata, 2011).

Studies often determine prostaglandin levels from urine samples, but Benedetti and colleagues (2014) have successfully measured short-term change in prostaglandins, including PGE_2, via salivary analysis among individuals exposed to a high-altitude environment where hypobaric hypoxia headache is more likely. Thus, systemic prostaglandin production can be measured to evaluate prostaglandin levels over time.

Emotional Pain, Stigma, and Obesity

While physical pain is typically characterized as negative sensations associated with disease, condition, or injury, emotional pain may be considered a sustained, distressing, and difficult to tolerate experience related to the self or perceived abilities (Meerwijk & Weiss, 2011; Merskey & Bogduk, 1994). Emotional pain, like physical pain, may signal a threat to well-being; therefore, acute emotional pain may signal a disruption in psychological state that helps individuals recognize a need to shift focus onto restoring well-being (Meerwijk & Weiss, 2011). However, chronic emotional pain results when adequate levels of self-efficacy, meaning, or social support cannot be maintained. Emotional pain also may result from negative evaluation of self and/or of social relationships with others (Athey & Overholser, 2016; Eisenberger & Lieberman, 2004). Both chronic physical pain and chronic emotional pain are related to feelings of hopelessness and incompetence (Jackson et al., 2014; Mee et al., 2011). Emotional pain also may occur in the context of conditions with heightened rates of physical pain; for example,

higher rates of depression are observed in patients with musculoskeletal conditions who report high levels of physical pain (Linton et al., 2011).

Stigma is a common type of emotional pain with a social basis (i.e., social pain). Indeed, stigma may be considered a social process whereby an individual is assigned negative attributes based on possession of an undesirable characteristic (Goffman, 1963). Stigma commonly has been studied in a number of contexts (e.g., mental health, race), but substantial research has addressed weight stigma in the context of overweight and obesity. Weight stigma is a form of social rejection, which itself is positively associated with physical pain (Eisenberger, Lieberman, & Williams, 2003). Many western societies, including the United States, tend to view overweight and obesity as an undesirable characteristic because these body types are not consistent with the socially-defined concepts of beauty. Indeed, several studies have documented individuals with obesity as being rated less attractive than individuals with average weight (Puhl & Heuer, 2009). Among individuals with overweight or obesity, weight stigma may be triggered by exposure to stigmatizing experiences via images or social interactions reminding the individual that their weight is not considered to be socially acceptable.

Three forms of stigma have been identified in the realm of weight stigma: experienced weight stigma, perceived weight stigma, and internalized weight stigma. Experienced weight stigma is defined as a clear act of weight-related discrimination towards an individual, such as being denied entry to an event due to excess weight. Perceived weight stigma is operationalized by the individual feeling discriminated against due to a weight-related comment or action by another, regardless of whether or not it was the intention of the speaker (e.g., doctor informing their patient that their BMI is categorized as overweight). Internalized weight stigma refers to the degree to which an individual believes negative weight-related attributes and/or stereotypes (e.g.,

laziness, lack of intelligence, moral weakness) are true and applicable to themselves. These internalized attributes and stereotypes often may be negative attributes and stereotypes ascribed by society to individuals with higher body weights (Puhl & Heuer, 2009).

Recent studies have highlighted the prevalence of internalized weight stigma in particular, and its negative impacts among individuals with overweight or obesity. In a sample of over 3,500 adults with BMIs ranging from underweight to obese, approximately 20% endorsed elevated levels of internalized weight stigma as measured by the Modified Weight Bias Internalization Scale (Puhl, Himmelstein, & Quinn, 2018), with those with higher BMIs endorsing greater internalization. Additionally, 52% of individuals recruited from an obesity-specific source, the Obesity Action Coalition (OAC), endorsed elevated internalized weight stigma scores, while only 18-20% of the non-obesity-specific sources endorsed elevated internalized weight stigma scores. The authors noted their results suggest a considerable portion of the population may be at risk for weight bias internalization, especially if they share certain characteristics often endorsed by the OAC subsample such as higher BMI, greater exposure to weight stigma, and attempting to lose weight.

In an online experimental study concerning experiences and attitudes related to having excess weight, 260 community-residing adults with overweight or obesity were randomized to one of two induction conditions: experience or internalization of weight bias (Pearl & Puhl, 2016). Participants in both groups began by reading a vignette describing a scenario in which an employee was denied a promotion at work due to being overweight. Following the vignette, participants completed two factual questions about vignette content to ensure they read it, and those who answered at least one question incorrectly were excluded from the study. Additionally, participants were asked to provide a rating on a seven-point scale of how qualified

and deserving the employee was of the promotion they were denied, with higher (greater number) ratings indicating greater perceived qualification and deservedness. Participants who reported ratings of one to three were excluded from the study, while those reporting ratings of four or greater were permitted to proceed as such ratings established that the participant perceived the employee to have experienced discrimination. Following these questions, participants in the experience condition read that the employee was upset due to their unfair treatment and were asked to write two to three sentences about a time when they experienced unfair treatment due to their weight. Participants randomized to the internalization condition read that the employee blamed themselves for being denied the promotion and felt worthless, as though they would not amount to anything due to their weight. Participants were then asked to write two to three sentences about a time they had similar thoughts and feelings about themselves due to their weight. Thus, although both conditions were designed to induce negative affect, the former encouraged the participant to focus on a triggering external event while the latter encouraged the participant to focus on personal thoughts and feelings. In the final portion of the online study, participants completed a series of self-report measures assessing affect, self-esteem, and weight bias internalization. Results indicated that the internalization condition was associated with more negative outcomes than the experience condition, including greater negative affect, less positive affect, lower self-esteem, and greater weight bias internalization. Thus, weight bias internalization is associated with negative affect and lower self-esteem among individuals with overweight or obesity, especially when focus is directed to weight stigma-related thoughts and feelings about the self.

Research suggests that there are significant physical and psychological risks associated with weight stigma, including increased risk of depression, lower self-esteem, greater anxiety,

poorer body image, and suicidality (Schvey, Puhl, & Brownell, 2011). Weight stigma is also associated with unhealthy eating behaviors, such as eating in secrecy, refusing to diet, losing sense of control over eating, and binge eating. Weight stigma also may interfere with one's motivation to engage in behaviors that would facilitate weight loss such as exercise and general physical activity. Indeed, among individuals enrolled in behavioral weight loss programs, greater weight stigma is associated with less energy expenditure during exercise, greater caloric intake, greater program attrition, and less weight loss (Carels et al., 2009). Although the mechanisms in these relationships are unknown, Carels and colleagues postulate that negative implicit and explicit weight-related attitudes held by those attempting to lose weight, negative affect, low self-efficacy, and/or low social support may be relevant. To further illustrate the problematic relationship between obesity and weight stigma, Tomiyama (2014) constructed the cyclic obesity/weight-based stigma (COBWEBS) model. This model specifically illustrates a negative, cyclical interaction between obesity and weight stigma. Tomiyama theorized that a positive feedback loop exists in this cycle such that weight stigma, an inherently negative emotional experience, contributes to weight gain through increased stress. The model illustrates how experiencing the stress of weight stigma is associated with behavioral (e.g., increased eating; Adam & Epel, 2007), biochemical (e.g., increased cortisol secretion; Schvey, Puhl, & Brownell, 2014; Tomiyama et al., 2014), cognitive (e.g., reduced executive control; Major, Eliezer, & Rieck, 2012), and physiological (e.g., sensitization to food reward; Adam & Epel, 2007) reactions that may directly or indirectly contribute to weight gain and impair weight loss, thus increasing likelihood of encountering future experiences that may trigger weight-based stigma (Tomiyama, 2014).

Recent research has examined the relationship of bodily pain to obesity and weight stigma. Pearl and colleagues (2016) found a positive relationship between internalized weight stigma and self-reported bodily pain among individuals with obesity (mean BMI = 42.2±12.1) seeking treatment for binge eating disorder. Recent research by Olson and colleagues (2018) has built on this finding in a sample of overweight and obese women enrolled in a weight loss intervention addressing body image. Results of their study revealed a positive relationship between BMI and bodily pain. In addition, both perceived and internalized weight stigma were associated with bodily pain. Among the overweight (BMI 25-29.9) subsample, perceived weight stigma mediated the relationship between BMI and bodily pain, but internalized weight stigma did not.

Pain Processing in the Brain

Often individuals who experience emotional pain such as social rejection describe their pain with words that are commonly used to describe physical pain (e.g., "hurt," "wounded;" DeWall et al., 2010). Interestingly, commonalities between physical and emotional pain may extend beyond descriptive terminology. It has been suggested that the neurobiological systems through which physical pain is processed may be the same mechanisms through which emotional pain is processed (Eisenberger & Lieberman, 2004).

Contemporary research has utilized neuroimaging techniques to evaluate the commonalities between emotional and physical pain. These studies have implicated the dorsal anterior cingulate cortex (dACC) and anterior insula. Increased activation is observed in these brain areas during both emotional (e.g., social rejection, social loss) and physical pain experiences (DeWall et al., 2010). In nonhuman primate research, lesions to the dACC and ventral anterior cingulate cortex are associated with reduced distress vocalizations after

separating animals from their caregiver or social group, whereas stimulation of these brain areas elicits greater distress vocalizations. Similar observations have been made in human subject studies. Increased activity of the dACC and anterior insula is observed among individuals following social rejection during a virtual ball-tossing game (Eisenberger et al., 2003); and bereaved individuals viewing pictures of the deceased exhibit increased activation in the dACC and anterior insula (O'Conner et al., 2008)

Thus, the literature supports the assertion that there are shared pathways involved in emotional/social and physical pain processing. In turn, it is possible that emotional pain, such as social rejection or weight stigma, could potentiate or exacerbate the experience of physical pain. Thus, methods for alleviating physical pain may be useful in addressing emotional pain such as social rejection or weight stigma.

Pain Management

Given the prevalence of chronic pain and its association with several negative physical and psychological health outcomes, identifying and disseminating effective pain management methods is of utmost importance. The goal of pain management is to modulate the experience of pain or response to pain using one or more approaches (e.g., pharmacological, behavioral) in order to reduce the pain as much as possible, or to improve self-efficacy in pain management (Takai, Yamamoto-Mitani, & Suzuki, 2015).

Several psychological strategies have been identified that are effective for pain management in a variety of conditions. Biofeedback and mindfulness-based stress reduction are two examples of strategies that may be delivered on their own to aid in pain management, but also are commonly delivered in conjunction with other forms of pain management. Broadly, these approaches help the patient react to, and cope with, physical pain and any accompanying

emotional pain in a more adaptive manner (Hylands-White, Duarte, & Raphael, 2017). Cognitive behavioral therapy (CBT) is a psychological approach to pain management that encourages patients to re-conceptualize their experience of pain symptoms in order to develop more realistic perceptions, adaptive behaviors, and positive functioning. Patients are encouraged to exert control over pain symptoms by employing cognitive and behavioral skills. Although CBT does not usually reduce pain per se, it is associated with improved self-efficacy and quality of life, and reduced distress (Hylands-White, Duarte, & Raphael, 2017).

Many researchers have studied the effectiveness of pharmacological therapies for chronic pain. This approach is an effective pain management strategy for many individuals with chronic pain, but adverse side-effects of long-term pharmacological therapy use have been reported (Finnerup, Sindrup, & Jensen, 2010; Planton & Edlund, 2010). Despite these risks, pharmacological therapy is still often used as a stand-alone treatment for chronic pain or in conjunction with other pain management methods. In treating pain with pharmacology, physicians may follow a system that matches, or is similar to, the World Health Organization (WHO) analgesic ladder (Ventadridda, Saita, Ripamonti, & De Conno, 1985). This system was initially developed for treatment of cancer pain, but can be applied to most pain conditions, and suggests that analgesic medications should be administered with increasing potency until the individual achieves pain relief (World Health Organization, 2015). It is suggested that pain relief efforts begin with administration of non-steroidal anti-inflammatory drugs, which share similarities with acetaminophen in that they produce pain relief via reductions in inflammation and products of inflammation (e.g., prostaglandins). Should this not achieve pain relief, weak opioids may be considered, with strong opioids serving as a last resort. Additionally, corticosteroids such as prednisone and dexamethasone may be used as adjuvant analgesics due to

their anti-inflammatory properties. Corticosteroids have been found to provide pain relief in a variety of conditions such as neuropathic and bone pains (Vyvey, 2010).

One of the most popular analgesics for acute and chronic pain in the United States is acetaminophen, the active ingredient in Tylenol. An estimated 23% of adults in the U.S. consume a drug that contains acetaminophen on a weekly basis (Kaufman, Kelly, Rosenberg, Anderson, & Mitchell, 2002). The effectiveness of acetaminophen in treating pain has been documented in several randomized controlled trials among patients with chronic or acute pain (e.g., arthritic, postoperative), as well as among adults with experimentally-induced pain (e.g., cold pressor; Mischkowski, Crocker, & Way, 2016). The mechanism through which acetaminophen provides pain reduction is uncertain, but it is widely accepted that pain reduction occurs via mechanisms in the central nervous system such as the dACC and anterior insula (DeWall et al., 2010) which are known to play a role in emotional, and particularly social, pain.

Due to the association of pain with obesity, several pain management approaches have been tested for their effectiveness in individuals with obesity. Weight reduction via diet and exercise have been associated with improved quality of life and reduced bodily pain in patients with obesity suffering from fibromyalgia (Senna, Sallam, Ashour, & Elarman, 2012), and weight reduction has been associated with diminished pain and improved physical performance among patients with obesity suffering from knee osteoarthritis (Messier et al., 2004). Physical rehabilitation via physical exercise (including aquatic therapy) has facilitated reductions in pain (Narouze & Souzdalnitski, 2015). Other strategies noted to reduce pain among individuals with obesity include acupuncture, CBT, and patient education regarding adaptive lifestyle changes to facilitate weight loss and better pain management (Narouze & Souzdalnitski, 2015). Pharmacotherapy also may be utilized to help patients with obesity manage pain. Medications

such as gabapentin or pregabalin may help patients with obesity and pain maintain activity levels to help prevent significant weight gain (Cabrera et al., 2012). Duloxetine also may help patients with obesity cope with pain from fibromyalgia, chronic musculoskeletal pain, and peripheral neuropathic pain from diabetes (Narouze & Souzdalnitski, 2015). Long-term opioid use is not recommended for patients with obesity due to lack of efficacy and safety concerns. Additionally, while adjuvant corticosteroids may assist with pain relief, common and problematic side-effects include increased appetite and weight gain (Vyvey, 2010).

Acetaminophen and Emotional Pain

Research on pain medications such as acetaminophen has traditionally examined physical pain, but recent studies documenting the overlap in physical and emotional pain processing have led to examining the effects of acetaminophen on emotional pain. An early study provided evidence that acetaminophen reduces social pain among healthy undergraduate students (DeWall et al., 2010) who were randomly assigned to receive 1,000mg of acetaminophen daily (500mg pill upon waking and 500mg pill one hour before bedtime) for three weeks, or placebo pills to be taken for the same amount of time in the first of two experiments. At the end of each day during the three-week period, participants rated total social pain experienced during that day. Results indicated that social pain decreased over the three-week span for those taking acetaminophen, but ratings did not change in the placebo group. In the second experiment conducted by DeWall and collages (2010), participants were randomly assigned to receive 2,000mg of either acetaminophen or placebo in pill form for three weeks, after which they completed a social exclusion task while undergoing an fMRI scan. Results indicated that participants who were randomly assigned to the acetaminophen condition exhibited less activity in the dACC and

anterior insula in response to social exclusion relative to participants assigned to the placebo condition (DeWall et al., 2010).

Whereas DeWall and colleagues studied only social pain, a more recent study examined the influence of acetaminophen on both positive and negative affect among undergraduate students (Durso, Luttrell, & Way, 2015) who were randomized to receive either an acute dose of acetaminophen (1,000mg) or placebo via liquid vehicle. After waiting 60 minutes, participants provided their emotional reactions to a series of pleasant and unpleasant images. Participants in the acetaminophen condition rated unpleasant images less negatively, but also rated positive images less positively, compared to those in the placebo condition. Those in the acetaminophen condition also rated images less emotionally stimulating than those in the placebo condition. Thus, the results suggest that acetaminophen may exert a blunting effect on processing of emotionally-provocative stimuli.

Other Psychological Outcomes

More recent research has sought to examine effects of acetaminophen on other psychological variables and processes. Roberts and colleagues (2017) investigated the impact of a 1000mg dose of acetaminophen versus a placebo on distrust, a common feature of borderline personality disorder (BPD) that can contribute to the interpersonal difficulties often observed among individuals with the disorder. Results revealed that distrust remained high among individuals with elevated BPD features who were administered a placebo, but increased trust was observed among those who were administered acetaminophen. Empathy also has been a focus of acetaminophen research, based on functional magnetic resonance imaging data suggesting that the brain areas (e.g., ACC, anterior insula) activated when experiencing pain are also activated when observing others experiencing pain (Lamm, Decety, & Singer, 2011). Mischkowski,

Crocker, and Way (2016) found that 1,000mg of acetaminophen reduced empathy for another's pain. Participants were administered acetaminophen or a placebo, after which they read a passage about someone experiencing social or physical pain, observed an individual being ostracized, or observed someone receiving a painful noise blast. Those administered acetaminophen reported less empathy in response to pain observed in another or pain they read about another receiving. When participants were exposed to a painful noise blast themselves, acetaminophen was associated with lower ratings of unpleasantness compared to the placebo condition.

Thus, acetaminophen has been associated with decreased social pain and reduced negative affect (DeWall et al., 2010; Durso et al., 2015). Such findings may be particularly relevant for individuals with overweight or obesity who are more likely to experience the social pain of weight stigma. However, no study has explored the effects of acetaminophen on the emotional pain of weight stigma among individuals with overweight or obesity. Although previous research has demonstrated that the relationship between BMI and physical pain is mediated by perceived weight stigma among women with overweight (Olson et al., 2018), the sample was relatively small (total n = 61; overweight n = 26). Therefore, it is important to replicate this finding, as well as to further investigate in a larger sample the relevance of internalized weight stigma as a mediator in the BMI-bodily pain relationship. Additionally, the possible role of an analgesic such as acetaminophen in moderating the relationship among BMI, weight stigma, and bodily pain has not been explored.

Current Studies

Two studies are proposed. Study one will evaluate the influence of a weight stigma induction on inflammation, pain, and distress among women with overweight and obesity, and

whether that effect is moderated by consuming acetaminophen. This study also will evaluate the relationship between BMI and pain, the degree to which the relationship is mediated by weight stigma, and the degree to which acetaminophen moderates the weight stigma-pain relationship. Study two will evaluate whether inflammation, pain, and distress are equivalent among three groups exposed to a weight stigma induction: women with overweight and obesity following an acute dose of acetaminophen, women with overweight and obesity following an acute dose of a placebo solution, and women with normal weight following an acute dose of a placebo solution. Aims and hypotheses for both studies are described below, with hypotheses identified as 'primary' or 'secondary'. Primary hypotheses reflect essential research questions while secondary hypotheses are exploratory analyses considered to be less central to the objectives of the two studies.

Study One

Aim #1: Evaluate the interrelationship of variables including BMI, inflammatory markers, distress, pain, affect, weight stigma, exposure to weight-based stigmatizing experiences, impact of weight on quality of life, and health-related quality of life.

Primary Hypotheses:

1a) At baseline, BMI will be positively associated with prostaglandins, CRP, internalized weight stigma, perceived weight stigma, exposure to weight-based stigmatizing experiences, impact of weight on quality of life, pain, and negative affect; and negatively associated with health-related quality of life and positive affect.

1b) At baseline, levels of inflammatory markers (prostaglandins, CRP) will be positively associated with pain, negative affect, internalized weight stigma,

perceived weight stigma, impact of weight on quality of life, and exposure to weight-based stigmatizing experiences; and negatively associated with health-related quality of life and positive affect.

Secondary Hypotheses:

1c) The relationship between BMI and baseline pain will be mediated by experienced weight stigma (see Figure 1).

1d) The relationship between BMI and baseline pain will be mediated by perceived weight stigma (see Figure 2).

1e) The relationship between BMI and baseline pain will be mediated by internalized weight stigma (see Figure 3).

1f) Effects of the weight stigma induction on the relationship between BMI and post-induction pain will be mediated by internalized weight stigma (see Figure 4).

i. In this mediation model, the relationship between internalized weight stigma and post-induction pain will be moderated by acute acetaminophen ingestion (see Figure 5).

Due to the cross-sectional design of the study, exploratory analyses will be used to evaluate the three types of weight stigma (experienced, perceived, and internalized) as moderators in the relationship between BMI and baseline pain. Additionally, exploratory analyses will evaluate internalized weight stigma as a moderator in the relationship between BMI and post-induction pain, as well as the moderating effect of acute acetaminophen ingestion in this relationship (i.e., moderated moderation).

Aim #2: Evaluate differences in affect, physical pain, distress, and inflammatory markers among four groups: those exposed to the weight stigma induction with either (1) acetaminophen or (2) a placebo solution, and those exposed to the control induction with either (3) acetaminophen or (4) a placebo solution.

Primary Hypotheses:

2) Participants randomized to receive the weight stigma induction and placebo conditions will report greater physical pain, distress, and negative affect; lower positive affect; and higher levels of prostaglandins following completion of the induction compared to the other three groups. No differences are expected on these dimensions among the other three conditions.

Study Two

Aim #3: Evaluate differences in affect, physical pain, distress, and inflammatory markers among three groups exposed to a weight stigma induction: participants with overweight or obesity randomized to acetaminophen or a placebo solution, and a sample of adults with normal weight given a placebo solution.

Primary Hypotheses:

3a) Among the three groups post-induction, those with overweight or obesity randomized to the placebo condition will report greater pain, distress, negative affect, and prostaglandins; and lower positive affect than individuals with overweight or obesity randomized to acetaminophen or individuals with normal weight. No differences are expected in pain, distress, positive and negative affect, and prostaglandins between the overweight or obese/acetaminophen group versus the normal weight group.

Secondary Hypotheses:

3b) Individuals in the overweight or obese groups will report greater baseline pain, distress, internalized weight stigma, perceived weight stigma, exposure to weight-based stigmatizing experiences, impact of weight on quality of life, and negative affect; and worse health-related quality of life and positive affect compared to participants with normal weight. The overweight or obese group also will demonstrate higher levels of prostaglandins and CRP at baseline compared to the normal weight group.

Chapter 2: Methods

Participants and Recruitment

160 women who are categorized as overweight (BMI 25-29.9) or obese (BMI ≥ 30) will be recruited for study one and study two, and an additional 40 females with normal weight (BMI 18.5-24.9) will be recruited for comparison in study two. Women will be the focus of study because women report more weight-related stigmatization than men and are more likely to internalize weight stigma (Boswell & White, 2015). Participants will be recruited from multiple sources: the NIH-funded ResearchMatch database, an internet site designed to help research investigators identify potentially eligible participants; StudySearch, an internet site coordinated by the Ohio State University Center for Clinical and Translational Science that allows community-residing individuals to identify research studies for which they may be eligible; and MyChart for Recruitment, another recruitment service coordinated by the Ohio State University Center for Clinical and Translational Science that uses an Honest Broker to identify potentially eligible participants among those enrolled in OSU's medical MyChart system and sends those individuals a study advertisement. The Psychology 1100 Research Experience Program at Ohio State University will serve as another source of participants for both studies. Flyers advertising both studies will be placed in various locations on Ohio State University's Columbus campus and in the surrounding Columbus community. An additional source of participants with overweight or obesity for study one will be women enrolled in the "Living Well" program, a behavioral weight management program offered at The Ohio State University Center for Wellness and Prevention. All eligible participants for both studies will be women who are at least 18 years of age. Overweight or obese participants will be stratified by age (18-40 years vs. over 40 years) and BMI (BMI = 25-29.9 vs. BMI ≥ 30) for randomization into one of four study

conditions. Following recruitment of overweight or obese participants for studies one and two, a cohort of participants with normal weight will be recruited for study two.

Procedures – Study One (Participants with Overweight or Obesity Only)

Individuals who express interest in the study will be contacted via telephone to complete a brief, ten-minute prescreening assessment to evaluate eligibility for the study. Information concerning age and sex will be collected to determine eligibility. Information regarding pregnancy status also will be collected; those endorsing current pregnancy will be excluded due to possible harm of acetaminophen use. Additionally, information regarding vision deficits and reading level will be obtained; those reporting vision deficits that prevent reading (e.g., blindness) or reporting less than a ninth-grade reading level will be excluded due to the impact these factors would have on the individual's ability to read study vignettes and questionnaires. The Patient Health Questionnaire – 9 will be administered to assess for depressive symptoms; individuals scoring 15 or greater (i.e., moderate/severe depressive symptoms) will be ruled ineligible due to the potential influence of these symptoms on their reaction to study vignettes and responses to questionnaire items. Other exclusionary criteria are risk factors associated with acetaminophen use such as currently taking a drug containing acetaminophen, history of liver disorder and/or alcohol abuse, and allergic reaction to acetaminophen (Mischkowski et al., 2016). Individuals also will be asked for estimated height and weight measurements to ensure they are eligible for study one (i.e., BMI in the overweight or obese categories). Individuals reporting weights exceeding 400 pounds will be excluded due to limitations of the laboratory weight scale. Eligible women will be asked to refrain from consuming food for three hours prior to their participation in the study to facilitate drug absorption (Roberts et al., 2017).

Participants will have their height and weight measured by study personnel upon arrival to confirm the BMI estimate calculated in the prescreening. This information also will be used to confirm the participant's stratification group for randomization. Following completion of physical measurements, participants will read and sign a study consent form. Participants will be given a copy of the consent form to keep for their own records. Following completion of study consent, study personnel will collect blood and saliva samples from participants for CRP and prostaglandin measurements, respectively. Next, participants will be led by study personnel to a room where they will complete the remainder of the experiment. Upon arrival at the room, participants will be randomized to receive either 10mL of acetaminophen (100 mg/mL) in liquid suspension, or 10mL of placebo (microcrystalline powder) in the same solution. The acetaminophen or placebo solution will be given to participants in plain cups and they will be instructed to ingest the solution as quickly as they can. Consistent with prior studies evaluating the effect of an acute dose of acetaminophen on psychological outcomes, participants will be required to wait 60 minutes after administration of the acetaminophen or placebo solution to allow sufficient time for absorption (Durso et al., 2015; Randles et al., 2013). Immediately following administration of the solution, participants will be given a packet of self-report measures that will require approximately 25 minutes to complete and that they may work on while waiting the required 60 minutes for drug absorption. After completion of self-report measures, participants will be asked to remain seated quietly until 60 minutes following administration of the solution. After 60 minutes has elapsed, participants will then be randomized to a weight stigma induction or a control induction.

The internalized weight stigma induction for the current study was created by Pearl and Puhl (2016) and is referenced in the introduction portion of this proposal (see pages 10-11). The

weight stigma induction consists of two parts. First, participants will read a vignette describing a scenario in which an employee has been denied a promotion at their place of employment due to being overweight.

After reading the vignette, the piece of paper on which it is typed will be taken from the participant who will then answer two factual questions to ensure they read the vignette. Participants answering one or both factual questions incorrectly will be excluded from study analyses. Participants also will be asked to rate on a seven-point scale how qualified and deserving the employee was of the promotion they were denied, with higher scores reflecting greater perceived qualification and deservedness. Next, participants will be given another piece of paper expressing that the employee felt stigmatized due to their weight. Participants will then be instructed to write 2-3 sentences describing a time when they may have had similar thoughts and feelings about themselves due to their weight, if there has been such a time.

The goal of the control induction for the current study will be to mirror the procedures of the weight stigma induction but with material that is not likely to evoke positive or negative emotion. The control vignette only describes the procedures involved in a company's promotion process. After reading the vignette, the paper on which it is typed will be taken from the participant. Next, participants will answer two factual questions about the vignette to ensure they read it. Participants answering one or both factual questions incorrectly will be excluded from study analyses. Additionally, participants will rate on a seven-point scale how qualified and deserving the employee was of the promotion, with higher rating reflecting greater perceived qualification and deservedness. Following completion of these items, participants will be given another piece of paper and instructed to write 2-3 sentences describing whether they believe the promotion process described in the vignette is reasonable and how they would change it, if at all.

Immediately following completion of the weight stigma induction or control induction, participants will complete a second packet of self-report measures. Following completion of self-report measures, participants will be taken to the room where they began their visit for collection of a second saliva sample. Study personnel will then provide participants with study payment, inform them of the nature of the experiment, and debrief the participant. During debriefing, study personnel will ask the participant which solution (acetaminophen or placebo) they believed they consumed earlier in the session, and will record their answer. The visit will then be concluded. Table 1 illustrates the study conditions and participant groups included in study 1, and a flow diagram of the experimental sessions is shown in Figure 6.

Procedures – Study Two (Participants with Normal Weight Only)

Prescreening procedures for study two will be identical to study one but with one addition. Individuals recruited for the normal weight group will be screened for history of overweight or obesity. Those endorsing a history of overweight or obesity will be excluded from the study due to their weight history potentially affecting their perceptions of weight stigma. BMI will be calculated using participant height and weight estimates to ensure that these individuals are in the normal weight range (i.e., BMI 18.5-24.9).

Procedures prior to the induction will be the same in study two as in study one, with one important exception. Rather than randomization to acetaminophen or placebo solutions, all participants with normal weight will receive the 1,000mg placebo solution. Participants will still wait 60 minutes before proceeding to the induction task, during which they will complete the same self-report measures as those completed by participants in study one at baseline.

Participants in study two will not be randomized to a weight stigma induction or control induction; instead, all participants will be exposed to the weight stigma induction. All other

procedures during and after the induction will be the same for study two as in study one. Table 2 illustrates the study conditions and participant groups included in study 2.

Measures

All participants in both studies will complete a demographic and medical history questionnaire which will include information regarding age, gender, marital status, race, level of education, current employment, health history, personal weight history, and relationships with individuals with overweight or obesity.

The following objective and self-report measures will be completed by participants in both studies:

Objective Measures:

Body Mass Index (BMI): Height and weight of each participant will be recorded. An individual's body mass index is a ratio of weight (in kilograms) divided by the square of height (in meters). It is a commonly used indicator of percentage of body fat. Height and weight will be measured with a portable stadiometer and a digital high-capacity scale.

Prostaglandins: Prostaglandin level (PGE_2) will be utilized as an objective marker of inflammation. Study personnel will first provide the participant with a small medicine cup of water which the participant will consume 10 minutes prior to saliva collection. During saliva collection, participants will be asked to provide saliva through a small straw which will funnel into a small test tube. The total amount of saliva needed is approximately half a teaspoon. Participants struggling to produce saliva may be encouraged to think about their favorite food or imagine tasting a lemon to increase saliva production. For saliva analysis, an assay similar to that used by Benedetti and colleagues (2014) will be used to measure prostaglandins per milliliter.

Prostaglandins will be measured twice: once upon arrival (baseline) and a second time at completion of the visit (post-induction). Salivary levels of prostaglandins will be measured using an ELISA kit from Cayman Chemical (Product No. 514010) and read on a Fisher Scientific Multiskan FC microplate reader.

C-Reactive Protein (CRP): CRP is found in blood plasma and will serve as another objective marker of inflammation. Study personnel will begin by cleaning a finger on the participant's non-dominant hand with an isopropyl alcohol wipe. Participants will then be asked to wave their hand to increase circulation to the area. Next, study personnel will use a contact-activated disposable lancet on the participant's finger in order to collect a blood sample. The lancet is designed to deliver a controlled, uniform puncture that provides a combination of sufficient capillary blood flow and minimal injury. Five blood drops from the finger will be applied to a blood spot card. Study personnel will facilitate the production of these blood drops by rubbing down on the participant's finger. Following collection of blood spots, the participant's finger will again be cleaned with an isopropyl alcohol wipe, and a bandage will be applied to the finger. CRP will be measured at baseline only. CRP (in milligrams per deciliter) will be measured in dried blood spots using the Meso QuickPlex SQ 120 (Meso Scale Discovery, 1601 Research Boulevard, Rockville, MD) with V-Plex kits purchased from Meso Scale Discovery. The average intra-assay coefficient of variation is 2.9% and the average inter-assay (run-to-run) coefficient of variation is 7.9%.

Primary Self-Report Measures

The following self-report measures will be completed using Qualtrics Survey Software at baseline and post-induction, unless otherwise noted. Participants may request to complete hard copy forms of the self-report measures if they prefer. Of note, weight stigma-related measures

will appear first in the order of measures to minimize the influence of those measures on the induction to which the participant is randomized. Additionally, all post-induction measures will be administered in random order:

Pain

*McGill Pain Questionnaire (*MPQ; Melzack, 1975): The MPQ is a measure designed to assess present aspects of pain (Pain Rating Index) and pain intensity (Present Pain Intensity scale) among adults. The Pain Rating Index contains 78 pain descriptor items that are grouped into four major pain subscales: sensory, affective, evaluative, and miscellaneous. Each descriptor has a value score assigned to it, with higher scores representing more severe pain. The Present Pain Intensity scale measures magnitude of overall pain intensity experienced by an individual, and includes six levels: none (0), mild (1), discomforting (2), distressing (3), horrible (4), and excruciating (5). Total Pain Rating Index scores range from 0-78 and Present Pain Intensity scores range from 0-5; in both scales, higher scores reflect greater pain severity. The MPQ has demonstrated good validity, reliability, consistency, and usefulness in assessing aspects of pain and pain intensity (Katz & Melzack, 2011).

Visual Analog Scale for Pain (VAS-Pain): The VAS-Pain is a unidimensional measure of physical pain intensity that has been used in a variety of adult populations. The continuous scale consists of a line 100 millimeters in length, anchored by two descriptors representing the extremes of pain (i.e., “no pain,” versus “my pain is as bad as it could possibly be”). Participants are asked to place a mark on the line to indicate their current level of pain. VAS-Pain scores are determined by using a ruler to measure the distance in millimeters between the “no pain” anchor and the participant’s mark. Scores range from 0-100, with higher scores indicating greater pain

intensity. The VAS-Pain demonstrates good test-retest reliability and construct validity. It is also sensitive to changes in pain assessed in intervals as short as one hour (Hawker et al., 2011).

Stigma

Stigma Situations Inventory (SSI; Myers & Rosen, 1999): The SSI is a 50-item questionnaire examining lifetime frequency of obesity-related experiences across eleven different categories: comments from children, from strangers, from family and from doctors; social exclusion; being stared at; loved ones being embarrassed by your size; negative assumptions that people make; physical barriers or obstacles; job discrimination; and physical violence. Respondents report frequency of each item on a scale of 0 (never) to 9 (daily). The mean of all items is typically used to measure overall frequency of weight stigma experiences, with greater values suggesting greater experience of weight stigma. The SSI has been utilized successfully as a measure of weight-based stigmatization, as well as consequences of those experiences (Vartanian, 2015). SSI will be measured once, prior to the induction task (baseline).

Weight Bias Internalization Scale (WBIS; Durso & Latner, 2008): The WBIS is an 11-item scale measuring the degree to which individuals believe that anti-fat attitudes are relevant to the self. Items are answered on a 7-point likert scale ranging from 1=strongly disagree to 7=strongly agree, with total scores ranging from 11 to 77. The WBIS has demonstrated high internal consistency and strong correlation with measures of drive for thinness, body image concern, and self-esteem (Durso & Latner, 2008). WBIS will be measured once, prior to the induction task (baseline).

Stigma Impact Scale (SIS; Fife & Wright, 2000): The SIS is a 24-item questionnaire that was originally developed to evaluate various facets of stigma and assess the impact of perceived

stigma among individuals with chronic illnesses. Each item is rated on a 5-point likert scale ranging from 0=not applicable to 4=strongly agree. The questionnaire includes four subscales representing social rejection, financial insecurity, internalized shame, and social isolation. Total scores range from 0 to 96. Subscale scores range from 0 to 36 for 32 social rejection, from 0 to 12 for financial insecurity, from 0 to 20 for internalized shame, and from 0 to 28 for social isolation. The term 'illness' will be changed to 'condition' to increase applicability of item content for participants in this study. Previously published data from our lab has demonstrated high reliability when following this procedure (Cronbach's alpha = 0.93; Olson et al., 2018).

Quality of Life

Medical Outcomes Survey, Short Form-36 (SF-36; Ware & Sherbourne, 1992): The SF-36 is a 36-item measure of health-related quality of life. Two composite scores can be generated: the mental component score (MCS) and the physical component score (PCS). T-scores are generated for component scores. The physical component score is heavily weighted by four subscales assessing physical functioning, physical role functioning, general health, and bodily pain, the latter of which will be utilized as another measure of baseline pain in analyses. The mental component score is heavily weighted by four subscales assessing vitality, social role functioning, emotional role functioning, and mental health. Each component score is transformed into a 0-100 scale with higher scores indicating better health-related quality of life. The SF-36 is an internationally-validated instrument for measuring health-related quality of life and has been utilized in a variety of sample types, including individuals with obesity (Callegari, Michelini, Sguazzin, Catona, & Klersy, 2005; Emery et al., 2015). SF-36 will be measured once, prior to the induction task (baseline).

Impact of Weight on Quality of Life-Lite (IWQOL-L; Kolotkin, Crosby, Kosloski, & Williams, 2001): The IWQOL-Lite is a 31-item measure of obesity-related quality of life. Each item is rated on a five-point Likert scale. Total scores range from 31 to 155 with higher scores reflecting greater impact of weight on quality of life. Also, five subscales can be scored for the IWQOL-Lite: physical function, self-esteem, sexual life, public distress, and work. The IWQOL-Lite has been tested in various samples, such as community-dwelling individuals with overweight or obesity, and has demonstrated good psychometric properties including high internal consistency, test-retest reliability, convergent validity, and discriminant validity (Kolotkin & Crosby, 2002). IWQOL will be measured once, prior to the induction task (baseline).

Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988): The PANAS is a 20-item measure of positive and negative affect. Each item is a single word reflecting an emotion (e.g., proud, excited, ashamed, upset) and respondents use a five-point Likert scale to indicate the degree to which they are experiencing each emotion during the present moment. Total scores for the negative affect and positive affect subscales range from 10-50. The PANAS subscales have demonstrated strong internal consistency and discriminant validity (Watson, Clark, & Tellegen, 1988).

Visual Analog Scale for Distress (VAS-Distress): The VAS-Distress will be used to measure distress and will match the construction and scoring formats of the VAS-Pain. Instead of pain-related anchors, the VAS-Distress will be anchored with "no distress" and "as distressed as I could possibly be" descriptors.

Secondary Self-Report Measures

The following self-report measures serve multiple purposes, including distraction to participants

following completion of the weight stigma-related measures at baseline, helping characterize the sample, helping identify relevant variables that may need to be included as control variables in study analyses, and/or serving as manipulation checks. Timing of administration is specified in the description of each measure.

International Physical Activity Questionnaire – Short Form (IPAQ-SF; Craig et al., 2003): The IPAQ-SF measures physical activity and inactivity performed during the previous seven days. Respondents report the number of days, hours per day, and minutes per day in the last seven days they engaged in vigorous exercise, moderate exercise, walking, and sitting. The IPAQ-SF has demonstrated acceptable reliability and validity across diverse samples. IPAQ-SF will be measured once, prior to the induction task (baseline).

Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989): The PSQI is used to assess sleep behavioral (quality and disturbances) over a one-month interval. It has demonstrated strong internal consistency, and has shown good sensitivity and specificity in distinguishing good and poor sleepers. The PSQI yields a total score as well as the following seven subscales: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction. PSQI will be measured once, prior to the induction task (baseline).

Rosenberg Self-Esteem Scale (RSES; Rosenberg, 1965): The RSES is a 10-item measure used to assess overall self-esteem. Both positive and negative feelings about the self are measured. Items are answered on a Likert scale ranging from 0 (strongly agree) to 3 (strongly disagree), with higher scores indicating higher self-esteem. The scale has demonstrated good internal consistency. RSES will be measured once, prior to the induction task (baseline).

Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983): The HADS is a 14-item measure developed to assess depression and anxiety among non-psychiatric medical patients. Respondents are asked to rate each item on a scale ranging from 0 (not at all) to 3 (most of the time). The HADS consists of a total distress score ranging from 0-42, and two subscales consisting of seven items each: anxiety (HADS-A; range 0-21) and depression (HADS-D; range 0-21). Six items are reverse scored. In each subscale a score above 10 indicates clinically significant distress. The HADS is a validated measure with strong internal consistency in both overall and subscale measures (Bjelland, Dahl, Haug, & Neckelmann, 2002), and has been used in several studies involving overweight or obesity. HADS will be measured once, prior to the induction task (baseline).

Binge Eating Scale (BES; Gormally, Black, Daston, & Rardin, 1982): The BES is a 16-item questionnaire designed to assess the behavioral (e.g., large amount of food consumed), as well as the cognitive and emotional (e.g., feeling out of control while eating), features of binge eating in adults with overweight or obesity. Respondents select one of three or four response options coded 0 to 2 or 3, respectively. Scores are summed and range from 0 to 46, with higher scores reflecting more severe binge eating problems. Scores greater than 17 reflect moderate binge eating severity, while scores greater than 26 reflect severe binge eating problems. The BES has demonstrated good internal consistency in a variety of samples with overweight or obesity (Cotter & Kelly, 2017). BES will be measured once, prior to the induction task (baseline).

*Need Threat Scale (*NTS; van Beest & Williams, 2006): The NTS is a 12-item measure designed to assess one's need for belonging, self-esteem, control, and meaningful existence, each of which represent a subscale of the measure. Respondents indicate how they are feeling right now using a five-point Likert scale ranging from "not at all" to "very much so." The NTS has been used in

several studies on Cyberball-induced ostracism (e.g., Eisenberger et al., 2003) showing that such an induction threatens these needs. In addition to four subscale scores, a composite score is calculated by averaging responses across the 12 items. The NTS will be measured once, after the induction task (post-induction).

Buckley Scale (BS; Buckley, Winkel, & Leary, 2004): The BS is a 12-item measure designed to assess feelings of happiness, anxiety, anger, sadness, and hurt feelings in the present moment. The scale is composed of five subscales for these five domains of emotion. Respondents indicate the degree to which they endorse a particular feeling using a seven-point Likert scale ranging from "not at all" to "extremely." The BS will be measured twice, both before and after the induction task.

Vividness of Recall: A single-item measure will be administered to assess vividness of participants' recall of the instance when they themselves experienced weight stigmatization that they write about in the weight stigma induction. This single item is adapted from research by Valenti and colleagues (2011) and will be administered once, after the induction task (post-induction).

Sample Size Calculation

Sample size for this study was determined using G-Power 3.1. No reported studies on effects of acetaminophen on weight stigma among individuals with normal weight, overweight, or obesity are available; therefore, studies comparing the effects of acetaminophen versus placebo on other emotional outcomes (i.e., affect, empathy for pain) were utilized to help determine sample size for the current study. Data from Durso and colleagues (2015) revealed a medium effect size (Cohen's d = .55) for undergraduate students administered acetaminophen

(versus placebo) evaluating positive and negative images (as determined by the International Affective Picture System). Data from Mischkowski and colleagues (2016) also revealed a medium effect size (Hedge's g = .45) in a study of empathic concern for others' pain among undergraduate students administered acetaminophen versus placebo. Effect sizes from Durso et al. and Mischkowski et al. were transformed to Cohen's F in order to complete a priori power analyses for an analysis of covariance with fixed effects, main effects, and interactions. These effect sizes were used to calculate power with an alpha of .05, one numerator degree of freedom, four groups, and two covariates, indicating a total sample size of 106 to 156 would result in power of .80. This sample size recommendation is consistent with the acetaminophen studies that informed the sample size calculations for Durso et al. and Mischkowski et al.; those studies recruited 30 to 50 participants per condition.

Analyses also were conducted to estimate the effect size of the weight stigma induction. Because Pearl and Puhl (2016) compared WBIS scores after exposure to one of two weight stigma inductions, the effect size for the difference between the two inductions could not be utilized to determine sample size for the current study. Instead, the WBIS mean score after exposure to the internalizing weight stigma induction condition in their study was compared to baseline WBIS mean scores in other studies among participants with overweight and obesity (Durso, Latner, & Ciao, 2016; Lee & Dedrick, 2016; Pearl et al., 2018; Latner, Barile, Durso, & O'Brien, 2014) as well as similar, unpublished data from our lab. A range of effect sizes (f = .216 to .582) was revealed after calculating mean differences between baseline WBIS scores and the mean WBIS score from Pearl and Puhl (2016), with most indicating effect sizes at the higher end of the range. To obtain the most conservative estimate of sample size needed for the proposed study, one a priori power analysis was conducted for an analysis of covariance with

fixed effects, main effects, and interactions using an effect size of .216 with an alpha of .05, one numerator degree of freedom, four groups, and two covariates. The required total sample size was 171 in order to achieve a power of .80.

Study 2 introduces individuals with normal weight. Therefore, additional analyses were conducted to estimate the effect of body weight category on emotional and psychological outcomes. Vieira and colleagues (2012) evaluated differences in several emotional and psychological variables among women with normal weight, overweight, class I obesity (BMI 30-34.9), and class II obesity (BMI 35-39.9). Analyses revealed medium to strong effect sizes for greater weight-related quality of life (as measured by the IWQOL-Lite; f = .510), higher self-esteem (as measured by the Rosenberg Self-Concept/Self-Esteem Scale (Rosenberg, 1965); f = .324), and lower body image dissatisfaction (as measured by the Body Image Assessment Questionnaire (Williamson, Davis, Bennett, Goreczny, & Gleaves, 1989); f = .813) among individuals with normal weight compared to those with overweight. Effect sizes were larger when comparing the normal weight category to class I and II obesity categories. In another study, experience and internalization of weight stigma were assessed among individuals with underweight or normal weight and among individuals with overweight or obesity (Lee, Gonzalez, Small, & Thompson, 2019). Medium effect sizes were detected for greater stigma internalization (as measured by the WBIS; f = .339) and stigmatizing experiences related to weight (as measured by the SSI; f = .339) among individuals with overweight or obesity compared to those with underweight or normal weight. A third study revealed a medium effect size for greater psychological well-being (as measured by Ryff's assessment of psychological well-being (Ryff, 1989)) among women with normal weight compared to women with severe obesity (f = .286; Bookwala & Boyar, 2008). The aforementioned effect sizes were used in

conducting a priori power analyses for an analysis of covariance with fixed effects, main effects, and interactions with an alpha of .05, one numerator degree of freedom, three groups, and three covariates. The required total sample to achieve a power of .80 for study 2 ranged from 15 to 98. Therefore, the proposed sample size of 200 participants (40 per cell; 160 overweight and obese, 40 normal weight) should result in sufficient power for studies 1 and 2.

Data Analysis

Statistical Analysis Software (SAS 9.3) will be used to complete all analyses. For study 1, Pearson correlations and analysis of variance (ANOVA) will be used to evaluate the interrelationship of baseline variables (baseline prostaglandins and CRP, MPQ total score, total WBIS score, total SIS score, mean SSI score, total IWQOL score, SF-36 component scores and bodily pain subscale score, and the PANAS subscale scores) with demographic variables (age, race, BMI, and education). These analyses also will evaluate hypotheses 1a (BMI will be positively associated with prostaglandins, CRP, internalized weight stigma, perceived weight stigma, exposure to weight-based stigmatizing experiences, impact of weight on quality of life, pain, and negative affect; and negatively associated with health-related quality of life and positive affect) and 1b (prostaglandins and CRP will be positively associated with pain, internalized weight stigma, perceived weight stigma, exposure to weight-based stigmatizing experiences, impact of weight on quality of life, and negative affect; and negatively associated with health-related quality of life and positive affect).

To evaluate hypotheses 1c (the relationship between BMI and baseline pain will be mediated by experienced weight stigma), 1d (the relationship between BMI and baseline pain will be mediated by perceived weight stigma), 1e (the relationship between BMI and baseline pain will be mediated by internalized weight stigma), and 1f (the relationship between BMI and

post-induction pain will be mediated by internalized weight stigma), the PROCESS (Hayes, 2013) macro will be employed with 10,000 bootstrap samples and 95% confidence intervals. For hypotheses 1c-1e, PROCESS will be used to test SSI, SIS, and WBIS, respectively, as mediators in the relationship between BMI and baseline MPQ total score. PROCESS will be used again to test three identical models, with the exception that baseline SF-36 bodily pain subscale score will serve as the dependent variable. For hypothesis 1f, PROCESS will be used to test WBIS as a mediator in the relationship between BMI and post-induction VAS-Pain, controlling for baseline VAS-Pain, and again between BMI and post-induction MPQ total score, controlling for baseline MPQ total score. Hypothesis 1fi will be evaluated using PROCESS to test moderated mediation models in which the mediating relationships tested in hypothesis 1f are moderated by acetaminophen condition (acetaminophen or placebo). Also, ratings of the employee's deservedness of the promotion will be entered as a covariate in all analyses for hypotheses 1f and 1fi.

The PROCESS macro also will be utilized to conduct exploratory moderation analyses. Specifically, eight simple moderation models will be used to assess potential conditional effects of experienced, perceived, and internalized weight stigma on the relationship between BMI and baseline pain outcome variables (baseline MPQ total score and SF-36 bodily pain subscale score), as well as post-induction pain outcome variables (post-induction MPQ total score and post-induction VAS-Pain). Additionally, two moderated mediation models will be used to assess the potential conditional effects of drug condition (acetaminophen or placebo) and internalized weight stigma on the relationship between BMI and post-induction pain outcome variables (post-induction MPQ total score and post-induction VAS-Pain). Ratings of the employee's deservedness of the promotion and baseline pain scores will be entered as covariates in

exploratory analyses involving post-induction pain outcomes. All moderation and moderated-moderation analyses will be conducted utilizing 10,000 bootstrap samples.

To evaluate hypothesis 2 (participants randomized to receive the weight stigma induction and placebo conditions will report greater physical pain, distress, and negative affect; lower positive affect; and higher levels of prostaglandins following completion of the induction compared to the other three groups), a series of analyses of covariance (ANCOVAs) will be conducted using post-induction measures (prostaglandins, positive and negative affect subscales of the PANAS, VAS-Pain, and VAS-Distress) as dependent variables, controlling for the relevant baseline measure and ratings of the employee's deservedness of the promotion. Stigma condition (with two levels) and drug condition (with two levels) will be entered as class variables. Scheffe tests will be utilized to identify group differences in the presence of a significant interaction.

For study 2, a series of ANCOVAs will be conducted matching the format of hypothesis 2 to test the hypotheses that, among the three groups exposed to the weight stigma induction (two overweight or obese from study 1 and one normal weight from study 2) those with overweight or obesity randomized to the placebo condition will report greater physical pain, distress, negative affect, and prostaglandins, and lower positive affect post-induction than individuals with overweight or obesity randomized to acetaminophen or individuals with normal weight. No differences are expected in physical pain, distress, positive and negative affect, and prostaglandins between the overweight or obese/acetaminophen group versus the normal weight group (hypothesis 3a). Having a relationship with someone with overweight or obesity also will be controlled for due to its potential impact on perceptions of weight stigma. The class variable will represent three conditions: the two overweight and obese groups exposed to the weight

stigma induction in study 1, and the normal weight group exposed to the weight stigma induction with placebo solution in study 2. Scheffe tests will be utilized to identify group differences in the presence of a significant main effect. To evaluate hypothesis 3b (those in the overweight or obese groups will report greater baseline bodily pain, internalized weight stigma, perceived weight stigma, exposure to weight-based stigmatizing experiences, impact of weight on quality of life, prostaglandins, and CRP; and worse health-related quality of life compared to participants with normal weight), data from the two overweight or obese groups exposed to the weight stigma induction will be combined into one group. Next, a series of ANOVAs will be used to compare the overweight/obese group and normal weight group on baseline variables (prostaglandins, CRP, MPQ total score, VAS-Pain and VAS-Distress scores, IWQOL total score, SF-36 component scores and bodily pain subscale, and PANAS subscales). Three ANCOVAs will be used to compare the same groups on baseline WBIS total score, baseline SIS total score, and baseline mean SSI score. Having a relationship with someone with overweight or obesity will be controlled for in these two analyses given its potential impact on these weight stigma-related outcomes.

Implications

Results of this study will further explicate possible shared pathways by which physical and social pain are processed. Past research has documented change in prostaglandins in relation to inflammation, and the effect of analgesics on both. However, this study will contribute to understanding how prostaglandins such as PGE_2 change in response to the social pain of weight stigma. Additionally, results will contribute to knowledge on stigma, obesity, and pharmacological intervention by determining the degree to which acetaminophen may blunt the acute, negative effects of weight stigma among individuals with overweight or obesity. If an

effect is detected, results also will illustrate how prostaglandins change in response to acetaminophen in such a situation. If the evidence suggests that those with overweight or obesity administered acetaminophen have the same inflammatory, physical, and psychological responses to a weight stigma induction as individuals with normal weight, then this may provide rationale for further investigation into the mechanisms by which pharmacological interventions affect social pain, including weight stigma.

An additional, potential implication of the current study is further understanding weight stigma as a mediator in the relationship between BMI and pain. Specifically, should perceived weight stigma mediate the relationship between BMI and bodily pain (hypothesis 1d), the model described by Olson and colleagues (2018) will be corroborated. Although the model was only evident in the subsample of overweight participants, the proposed study is more adequately powered to test the model with a larger sample. Thus, this study may provide further evidence of internalized weight stigma mediating the BMI-bodily pain relationship (hypothesis 1d), as well as test the model in the context of experimental changes in pain (hypothesis 1e). Should this model be supported, further investigation will be needed of the relationship between weight stigma and bodily pain among individuals with overweight or obesity. It also would provide further rationale to investigate effects of interventions aimed at reducing weight stigma among individuals with overweight or obesity and bodily pain. In addition to interventions that directly target weight stigma, interventions may provide benefit by modulating the relationship between weight stigma and bodily pain. If drug condition (i.e., acetaminophen or placebo) moderates the influence of internalized weight stigma on bodily pain (hypothesis 1fi), results will enhance understanding of the mechanisms by which obesity is associated with bodily pain, and possibly contribute to future research into the mechanisms of these relationships.

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Appendix A: Tables and Figures

Table 1: Experimental conditions and participants in study 1 (N = 160)

Participants with Overweight or Obesity	
Acetaminophen + Control (n = 40)	Acetaminophen + Stigma (n = 40)
Placebo + Control (n = 40)	Placebo + Stigma (n = 40)

Table 2: Experimental conditions and participants in study 2 (N = 120)

Participants with Overweight or Obesity	Participants with Normal Weight
Acetaminophen + Stigma (n = 40)	Placebo + Stigma (n = 40)
Placebo + Stigma (n = 40)	

Data from these two groups from study 1 will be utilized for study 2.

Figure 1: Hypothesized model for experienced weight stigma as a mediator in the relationship between BMI and baseline bodily pain.

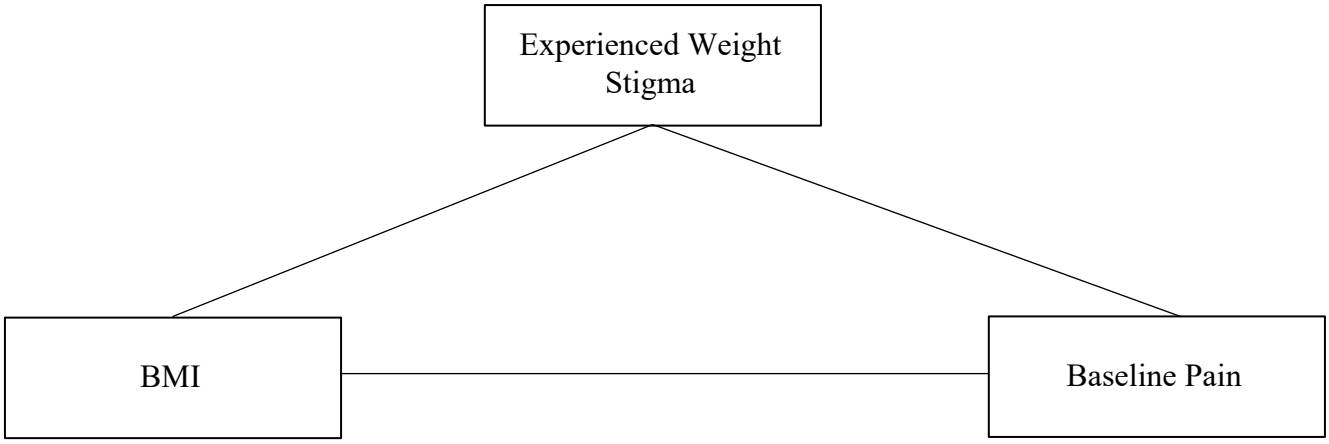

Figure 2: Hypothesized model for perceived weight stigma as a mediator in the relationship between BMI and baseline bodily pain.

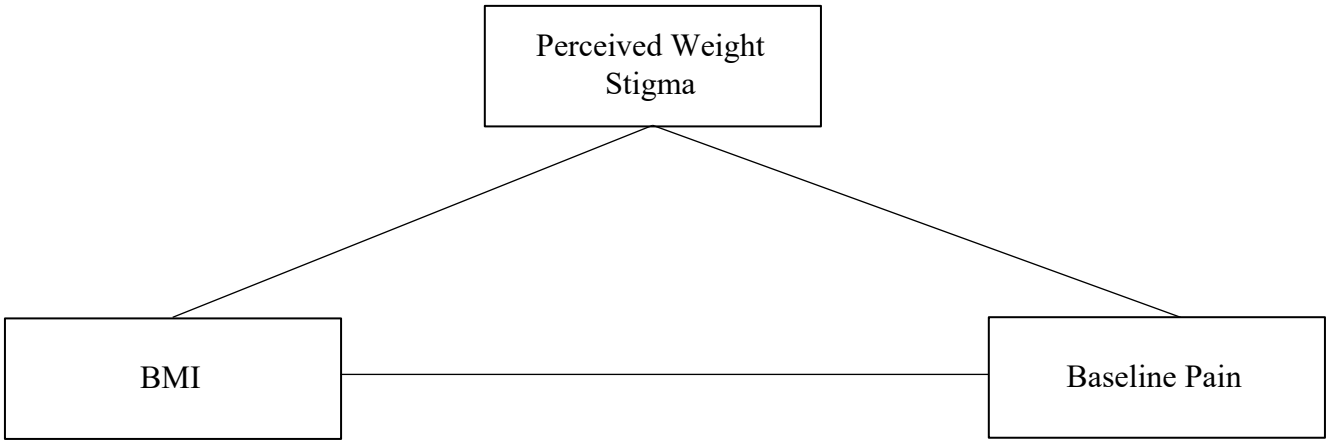

Figure 3: Hypothesized model for internalized weight stigma as a mediator in the relationship between BMI and baseline bodily pain.

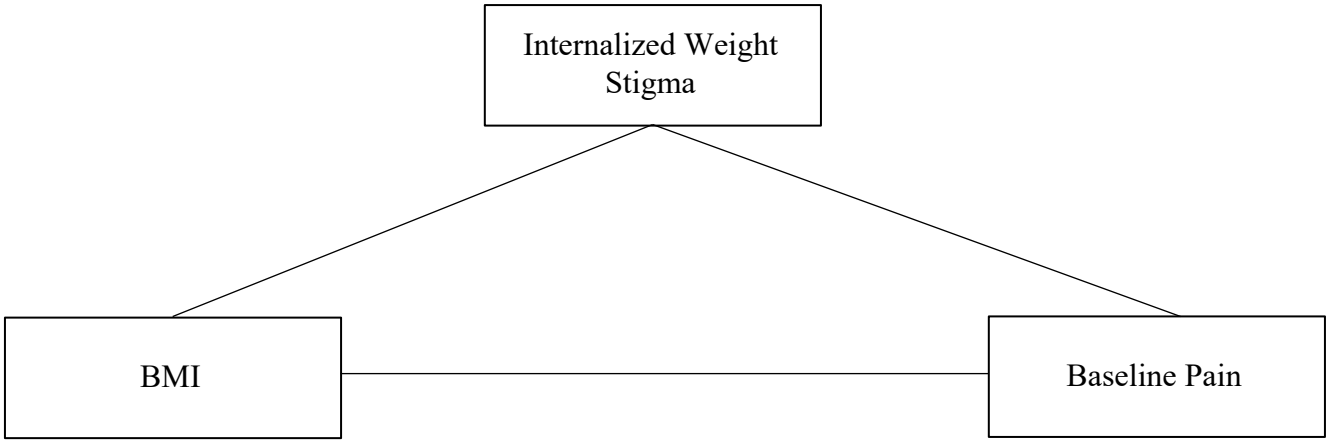

Figure 4: Hypothesized model for internalized weight stigma as a mediator in the relationship between BMI and post-induction pain.

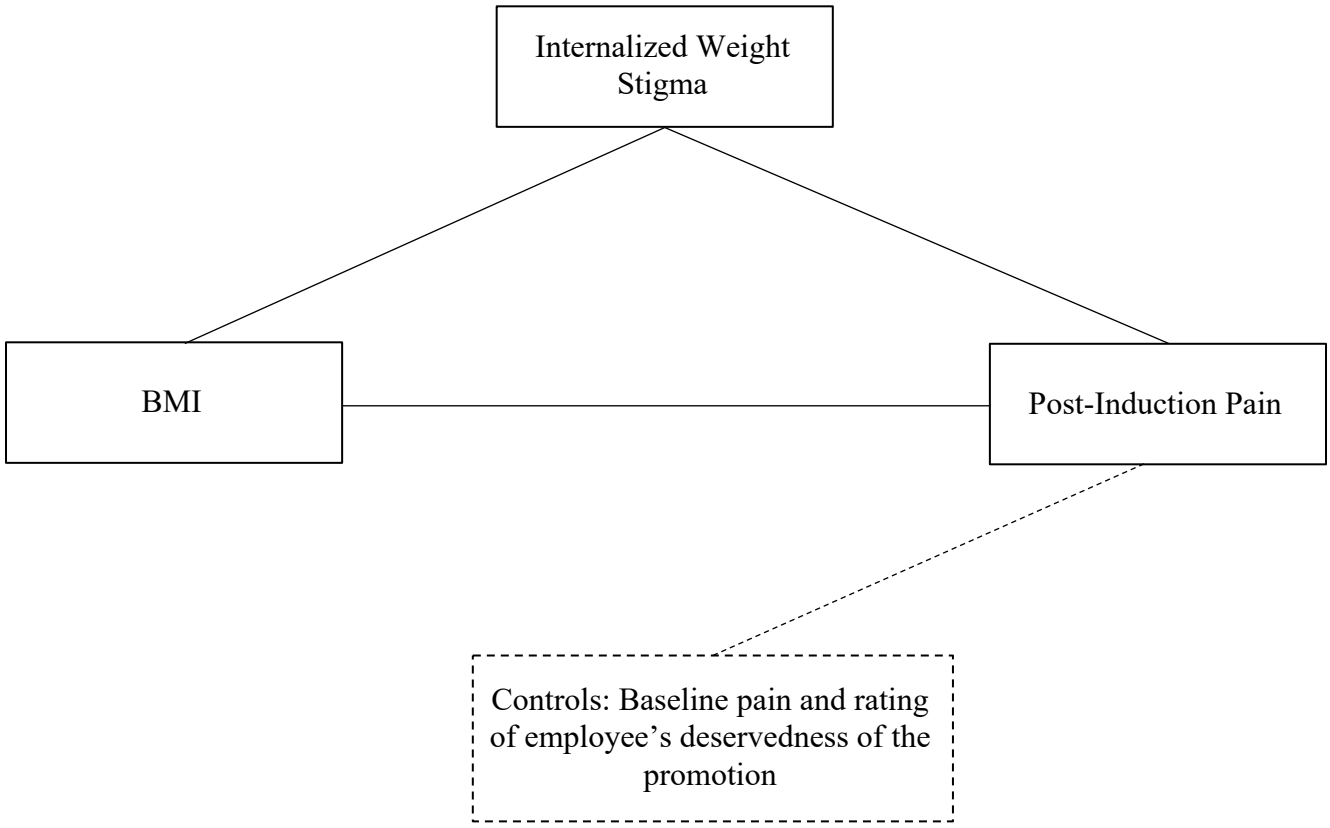

Figure 5: Hypothesized model for drug condition (acetaminophen or placebo) moderating the effect of internalized weight stigma as a mediator between BMI and post-induction pain.

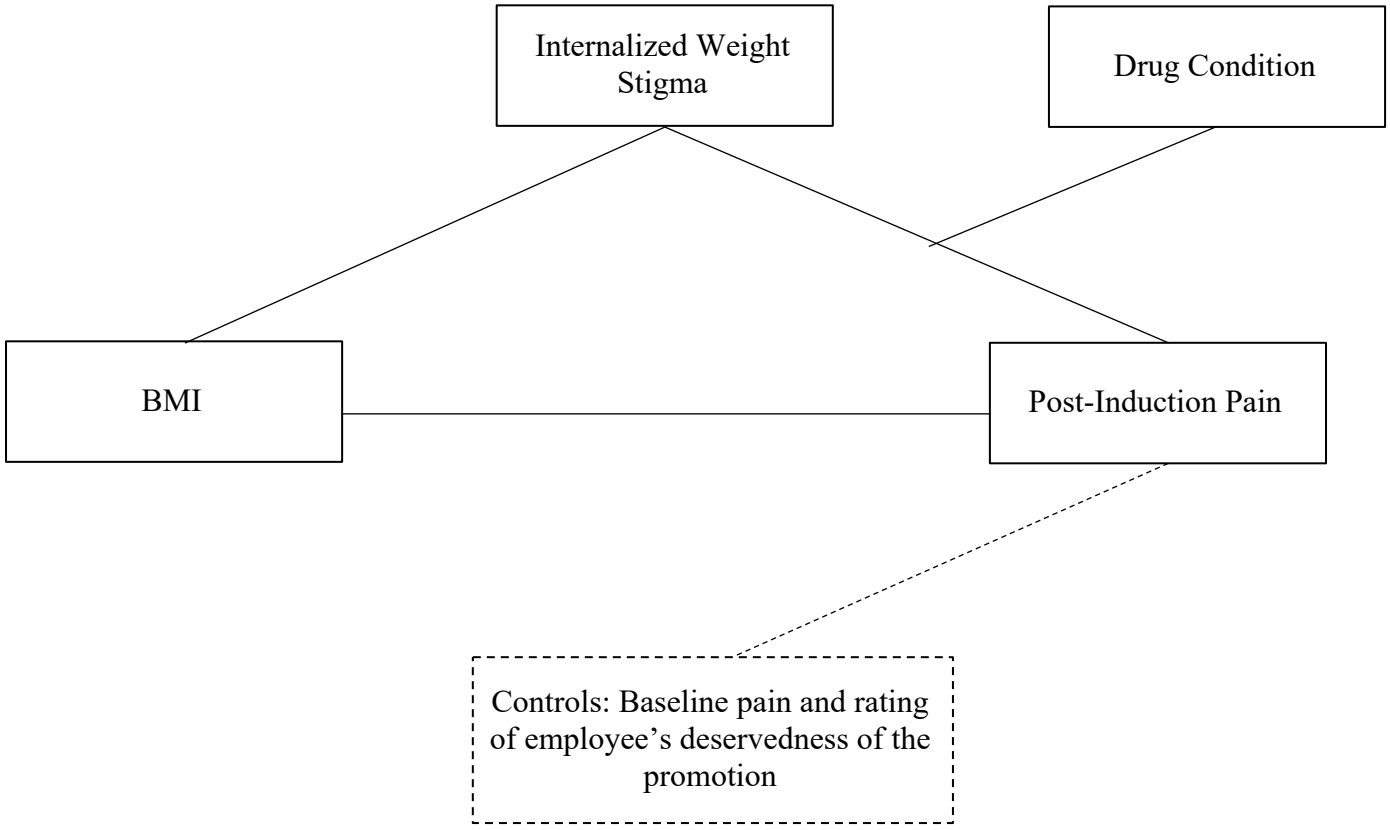

Figure 6: Flow diagram of experimental sessions (note: all participants with normal weight will be placed in the placebo and weight stigma condition)