DEPRESSION AND THE METABOLIC SYNDROME IN MIDDLE-AGED WOMEN: A LONGITUDINAL INVESTIGATION

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DEPRESSION AND THE METABOLIC SYNDROME IN MIDDLE-AGED WOMEN:

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Depression predicts increased risk of coronary artery disease and type 2 diabetes, and the metabolic syndrome (MS) is a putative link between depression and these diseases. There are no prospective studies of the effect of major depression on risk for the MS. This study examined the cross-sectional and longitudinal relationship of major depression with the MS, central adiposity, and insulin resistance (IR), over a period of 6 years. Data were drawn from the "Study of Women's Health Across the Nation", an ongoing, multi-site investigation of perimenopausal women. The sample included 421 women (34% Black), ages 42-52 (M = 45.6 $\pm$ 2.5) from the ancillary Mental Health Study of the participants from the Pittsburgh site. Major depression diagnosis (lifetime history and current), other diagnoses (anxiety disorders, substance abuse / dependence) and antidepressant use were collected annually via the SCID-IV. The MS was measured at baseline and bi-annually thereafter; WC and IR were assessed annually. Health behaviors included smoking (annually), and physical activity and diet (baseline). Logistic regression and survival analyses examined the odds/risk of developing the MS over the course of the study in the full sample and in women free of the MS at baseline. Generalized Estimating Equations (GEE) examined the relationship between depression (time-varying) and the MS (time-varying) over the course of the study. Exploratory analyses were conducted to examine whether associations were independent of demographics, diabetes, and other diagnoses, and to examine the association of depression with WC. Baseline depression predicted marginally greater odds of having the MS over the course of the study (cumulative index) in the full sample, independent of covariates. Women with baseline depression showed a trend for increased risk of developing the MS; this effect was not significant. GEE analyses showed no significant concurrent associations

between depression and the MS across time, suggesting that depression and the MS did not "track" together over time. Finally, baseline depression predicted greater WC at the final visit, although this was reduced after controlling for age and race. Findings suggest that major depression may be an important predictor of the prevalence and incidence of the MS in women.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

I would like to acknowledge The Study of Women's Health Across the Nation (SWAN), supported by the National Institutes of Health, DHHS, through the National Institute on Aging, the National Institute of Nursing Research and the NIH Office of Research on Women's Health (Grants NR004061; AG012505, AG012535, AG012531, AG012539, AG012546, AG012553, AG012554, AG012495), as well as the ancillary Mental Health Study (supported by the National Institute of Mental Health) for providing me access to the data for my dissertation. I would like to thank my advisor, Karen Matthews, for her guidance, wisdom, patience, and generosity in providing me with numerous opportunities for professional development and personal growth throughout my graduate career. I would also like to recognize the many staff and graduate students who are members of the Cardiovascular Behavioral Medicine laboratory and SWAN. Additionally, I would like to thank my committee members, Dr. Stephen Manuck, Dr. Marsha Marcus, Dr. Anna Marsland, and Dr. Joyce Bromberger, for their contributions to my professional development. I would also like to thank Dr. Ada Youk and Dr. Rebecca Thurston and for their guidance and feedback on this dissertation.

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1. INTRODUCTION

1.1 OVERVIEW

The metabolic syndrome is a cluster of anthropometric, metabolic and hemodynamic perturbations that have been linked to increased risk for Type 2 diabetes (Grundy, Brewer, Cleeman, Smith, & Lenfant, 2004), cardiovascular morbidity and mortality, and all-cause mortality (Ford, 2005b; Hansen, 1999; Sundstrom et al., 2006; Trevisan, Liu, Bahsas, & Menotti, 1998). To date, no consensus has been reached as to the definition of the metabolic syndrome. However, abnormal insulin or glucose regulation, dyslipidemia, central adiposity or obesity, and hypertension are consistently included in the most widely accepted definitions of the metabolic syndrome, proposed by the World Health Organization (WHO) (Alberti & Zimmet, 1998), the U.S. National Cholesterol Education Program Adult Treatment Panel III (ATP III) and the International Diabetes Foundation (IDF) (Alberti, Zimmet, & Shaw, 2005). It is hypothesized that visceral / central adiposity and insulin resistance / glucose intolerance are most likely the key components (Grundy et al., 2005; Miranda, DeFronzo, Califf, & Guyton, 2005), and affect risk via a number of physiological mechanisms, including nonesterified fatty acid liberation and adipokine (e.g., adiponectin) production (Carr et al., 2004), independent of obesity and other risk factors (Egan, Greene, & Goodfriend, 2001; Janssen, Katzmarzyk, & Ross, 2002). Nevertheless, some evidence exists that the convergence of these risk factors together represents a single cohesive syndrome which elevates one's risk for disease (Pladevall et al., 2006; Shen et al., 2003). Age-adjusted prevalence estimates for the metabolic syndrome in adults range from approximately 35% (using ATP III criteria) to approximately 40% (using IDF criteria), depending on the definition of impaired fasting glucose (Ford, 2005a). As a prevalent condition and important predictor of disease across race, gender, and age groups, the metabolic syndrome provides a unique opportunity for identifying high-risk populations and preventing the progression of more serious diseases. However, despite the potential implications of the metabolic

syndrome for overall health and disease prevention, the etiology of the metabolic syndrome remains unclear.

Interest in the role that psychological factors may play in the development and progression of the metabolic syndrome developed largely out of the extensive literature documenting the relationship between psychological variables and various disease outcomes, including coronary heart disease (CHD) and Type 2 diabetes, as well as the work of Bjorntorp and colleagues suggesting an association between chronic stress, visceral adiposity, and the metabolic syndrome (for reviews, see Bjorntorp, 2001; Bjorntorp & Rosmond, 1999). Studies of psychological characteristics and disease have shown that anger / hostility (Krantz & McCeny, 2002; Miller, Smith, Turner, Guijarro, & Hallet, 1996; Williams et al., 2000) and some forms of clinical anxiety (Kubzansky, Kawachi, Weiss, & Sparrow, 1998), predict cardiovascular morbidity and mortality, although contradictory findings have been reported (Everson et al., 1997; Leon, Finn, Murray, & Bailey, 1988; Rozanski, Blumenthal, & Kaplan, 1999). More consistent findings have been reported for depression, such that depressive illness as well as depressive symptoms predict increased risk for coronary disease and cardiovascular mortality (for reviews, see Grippo & Johnson, 2002; Joynt, Whellan, & O'Connor, 2003; Musante & Treiber, 2000; Wulsin, 2004) . Moreover, several meta-analytic reviews suggest that depression contributes a modest, but significant, independent risk for incident coronary disease (Rugulies, 2002; Wulsin & Singal, 2003), with one review showing that clinical depression was a stronger predictor of disease onset than depressive symptoms alone (Rugulies, 2002). Similar findings have been reported in the diabetes literature (for reviews, see Kawakami, Takatsuka, Shimizu, & Ishibashi, 1999; Musselman et al., 2003), such that depressive illness (Eaton, Armeniain, Gallo, Pratt, & Ford, 1996; Kawakami et al., 1999) and depressive symptomatology (Arroyo et al., 2004; Carnethon, Kinder, Fair, Stafford, & Fortmann, 2003) are associated with increased risk for incident Type 2 diabetes.

Despite substantial evidence for a role of depression in the pathogenesis of CHD and Type 2 diabetes, relatively few studies have directly addressed the relationship between depression and the metabolic syndrome. The existing literature is limited mostly to investigations of the association between depression and individual components of the metabolic syndrome, particularly central or visceral adiposity and insulin resistance. The majority of these studies have demonstrated a cross-sectional association of

depression or depressive symptoms with these particular components of the metabolic syndrome, especially in young adults; although, a few failed to find significant cross-sectional associations in middle-aged women. Prospective data are mixed, with several studies showing a positive association with central adiposity or insulin resistance, and others failing to find prospective associations with levels of central adiposity. Although these studies provide indirect support for the contention that depression is related to components of the metabolic syndrome, they are limited by mainly cross-sectional data and do not provide information about the relationship between depression and the clustering of these components to form the metabolic syndrome.

To our knowledge, only four studies have examined the relationship between depression or depressive symptoms and the metabolic syndrome in its entirety. Two studies, conducted with cross-sectional data, showed that depressive symptoms in men (McCaffery, Niaura, Todaro, Swan, & Carmelli, 2003) or a history of major depressive illness in women, but not men (Kinder, Carnethon, Palaniappa, King, & Fortman, 2004) was associated with increased risk for the metabolic syndrome. However, a third, cross-sectional study of depressive symptoms in young adults failed to find an association with central adiposity or the metabolic syndrome (Herva, Rasanen et al., 2006). In the only prospective study of the relationship between depression and the metabolic syndrome, Raikkonen, Matthews, and Kuller (2002) showed that women with higher baseline depressive symptoms had elevated risk for developing the metabolic syndrome over time, providing preliminary support for an association between depression and the metabolic syndrome in middle-age.

In aggregate, the data from these converging lines of research provide some preliminary evidence for the hypothesis that depression is related to elevated risk for the metabolic syndrome, particularly in women. However, the current literature is marked by several limitations. First, most of the data are cross-sectional and therefore provide no information about the direction of the relationship between depression and the metabolic syndrome. Moreover, self-report measures of depressive symptoms do not elucidate the nature of the relationship between depression, particularly depressive illness, and the metabolic syndrome. Despite the relevant physiological aberrations reported to accompany clinical depression and the growing evidence for a dose-response relationship between depression and CHD (Wulsin, 2004), only one study has investigated the relationship between clinical

depression and the metabolic syndrome (Kinder et al., 2004). Although this study provides preliminary evidence for a cross-sectional relationship between a history of major depressive illness and the metabolic syndrome in women, the data provide no information about direction of the association and do not account for the potential effect of time. We are unaware of any study to date that has prospectively examined the relationship between depressive illness and the metabolic syndrome.

Thus, the purpose of the current study is to investigate the cross-sectional and longitudinal relationship of depressive illness with the metabolic syndrome in a sample of women undergoing the menopausal transition. Importantly, the longitudinal nature of the data and the repeated measurements over time will permit closer examination of the association between clinical depression and the metabolic syndrome over time and test the hypothesis that depression precedes the metabolic syndrome. Given the evidence to suggest that insulin resistance and central adiposity are likely the core components of the metabolic syndrome, we will also examine the relationship of depression with waist circumference and an indicator of insulin resistance. Finally, we will explore whether these associations vary by race or menopausal status, and we will evaluate health behaviors as a possible mechanism linking depression with the metabolic syndrome. A model describing the hypothesized association between depression and the metabolic syndrome, as well as potential mediating and moderating pathways, is presented in Figure 1.

Prior to outlining the hypotheses and methodology of the current study, this paper will provide a historical context and rationale by presenting a brief summary of the following topics: (1) a description of the metabolic syndrome, its central physiological aberrations, and some of the factors believed to contribute to its development; (2) the history of psychosocial factors and the metabolic syndrome, emphasizing the evidence for a link between psychological indicators and the metabolic syndrome; (3) the relationship between depression and the purported core components of the metabolic syndrome, namely, central adiposity and insulin resistance; (4) available studies of depression and the metabolic syndrome and limitations of the current literature; (5) potential moderating factors of the relationship between depression and the metabolic syndrome.

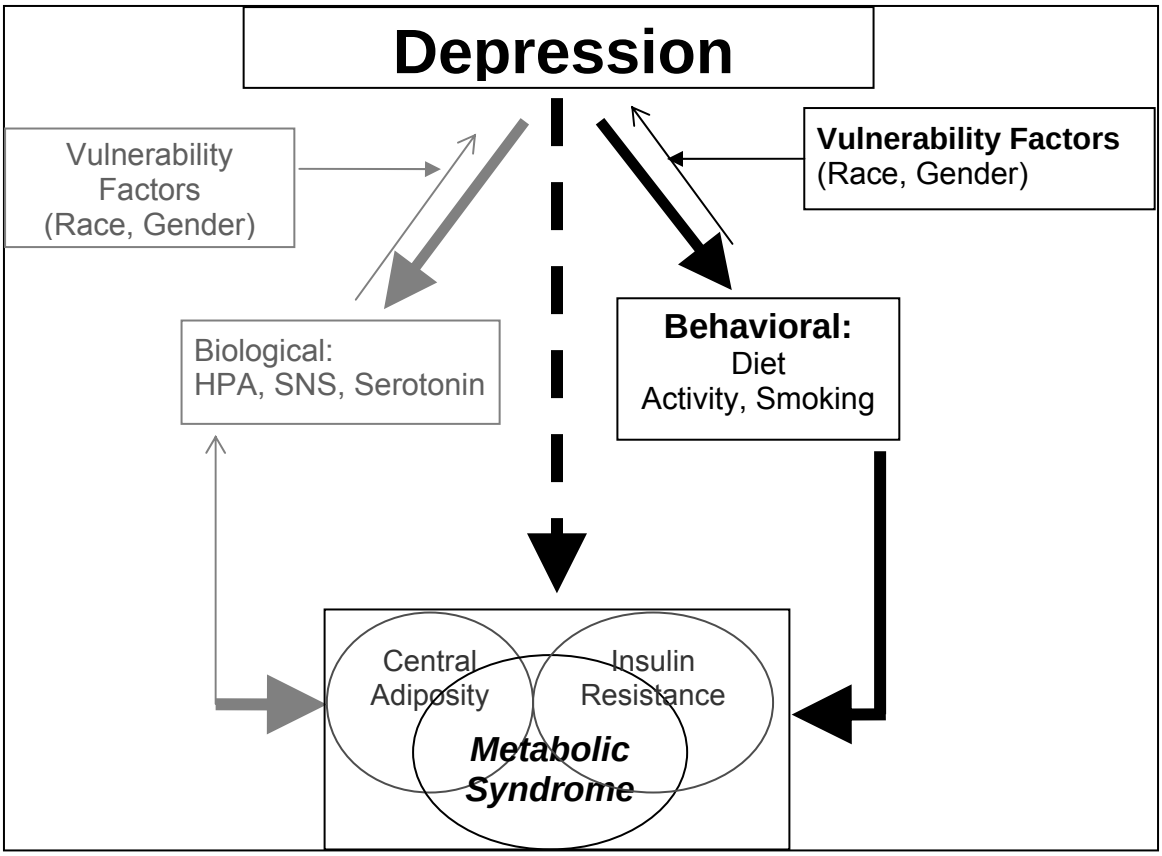

Figure 1: Model of the association between depression and the metabolic syndrome

1.2 THE METABOLIC SYNDROME

1.2.1 Background

Interest in the metabolic syndrome developed out of an observation that certain cardiovascular risk factors frequently co-occurred, and that these risk factors were both independently and cumulatively related to cardiovascular health (Reaven, Abbasi, & McLaughlin, 2004). Since that time, there has been a growing body of evidence for an association between the metabolic syndrome and disease, particularly CHD and Type 2 diabetes (Grundy, Hansen, Laaksonene, et al., 2002), independent of traditional risk factors (e.g., obesity). Although there is some debate about the best definition of the metabolic syndrome, the two most widely accepted definitions classify the metabolic syndrome based on the presence of three or more of the following physiological aberrations: abdominal / visceral adiposity, insulin resistance, hypertension, and dyslipidemia (Expert Panel on Detection, 2001). Given the insalubrious effects of insulin resistance and central adiposity on cardiovascular and metabolic health (Lapidus & Bengtsson, 1988; Larsson, 1988; Pouliot et al., 1992; Pyorala, Savolainen, Kaukola, & Haapakoski, 1985), some researchers have postulated that these constituents drive the heightened risk for disease (Anderson et al., 2001; DeFronzo & Ferrannini, 1991; Despres & Marette, 1994; Reilly & Rader, 2003). However, there is also fairly robust support for the assertion that the concurrence of the multiple risk factors represents one cohesive syndrome, and the syndrome itself is the best predictor of disease (DeFronzo & Ferrannini, 1991; Expert Panel on Detection, 2001; Shen et al., 2003).

It is hypothesized that psychological factors, in concert with or independent of genetic vulnerabilities (Bouchard, Despres, & Mauriege, 1993; Freeman, Mansfield, Barrett, & Grant, 2002; Groop & Ortho-Melander, 2001), may contribute to the pathogenesis of the metabolic syndrome through both physiological (e.g., hypothalamic-pituitary-adrenal (HPA) axis, sympathetic-adrenal-medullary (SAM) system) (Bjorntorp & Rosmond, 1999; Landsberg, 1999) and behavioral (e.g., diet, physical inactivity) pathways. Because of the extensive literature documenting the relationship between psychological variables and various disease outcomes, particularly those for which the metabolic syndrome is a putative risk factor, attention has turned to the role that psychological factors may play in the pathogenesis of the

metabolic syndrome. Notably, a better understanding of the relationship between psychological factors and the metabolic syndrome may identify the metabolic syndrome as a link between psychological factors and disease, especially CHD and Type 2 diabetes (Bjorntorp, 1990, 1991).

1.2.2 Psychosocial Factors and the Metabolic Syndrome

Literature on the relationship between the metabolic syndrome and psychological factors has evolved from several converging lines of research, including the chronic stress literature and studies of the Type A behavior pattern. For example, Bjorntorp has written fairly extensively about the hypothesis that chronic stress is related to the development of central adiposity and the metabolic syndrome (Bjorntorp, 1991, 1993, 1997, 1999, 2001; Bjorntorp & Rosmond, 1999). The assertion in these papers is that chronic exposure to stressors (including a variety of psychosocial and psychological factors) activates the HPA axis and related "stress centers" which, in turn, contribute to preferential fat deposition in the abdominal area and subsequent development of insulin resistance and other features of the metabolic syndrome. While relevant literature provides some empirical support for an association between chronic stress and central adiposity (e.g. Epel et al., 2000), psychological factors are often indiscriminately combined with other psychosocial vulnerabilities and discussed only within the context of stress.

Based on the hypothesis that the Type A construct confers increased risk for the development of CHD, a limited number of studies have investigated the association between Type A behavior and features of the metabolic syndrome (Keltikangas-Jarvinen, Raikkonen, & Hautanen, 1996; Keltikangas-Jarvinen, Raikkonen, Hautanen, & Herman, 1996). However, given the results of several epidemiological investigations which failed to find support for a relationship between the Type A construct and CHD (Dembroski, MacDougall, Williams, Haney, & Blumenthal, 1985; Matthews & Haynes, 1986; Shekelle et al., 1985), the majority of the focus shifted from the global Type A construct to more specific investigations of hostility and anger, as subsequent investigations revealed that these attributes may be the most critical components of the Type A behavior pattern (Dembroski et al., 1985).

Recent investigations of the relation of the metabolic syndrome with psychological factors have focused on more specific indicators of psychological functioning. For instance, several studies have

shown that anger, hostility, and anxiety are cross-sectionally associated with central adiposity (Kaye, Folsom, Jacobs, Hughes, & Flack, 1993; Niaura et al., 2000; Niaura et al., 2002; Scherwitz et al., 1992; Wing, Matthews, Kuller, Meilahn, & Plantinga, 1991) or insulin resistance (Surwit et al., 2002; Vitaliano, Scanlan, Krenz, & Fujimoto, 1996), the physiological aberrations hypothesized to be at the heart of the metabolic syndrome. There is also some evidence for a prospective relationship of anger or hostility with increased central adiposity (Raikkonen, Matthews, & Kuller, 1999; Raikkonen, Matthews, Kuller, Reiber, & Bunker, 1999) and risk for the full metabolic syndrome over time (Raikkonen, Matthews, & Salomon, 2003). However, results are not entirely consistent, as some studies have shown no association (Ravaja, Keltikangas-Jarvinen, & Viikari, 1996) or an inverse or bi-directional relationship (Nelson, Palmer, Pedersen, & Miles, 1999; Raikkonen et al., 2002).

1.3 WHY DEPRESSION?

1.3.1 Depression and Health

Numerous studies conducted with population-based samples have consistently demonstrated that a history of major depressive disorder confers increased risk for the development of CHD and Type 2 diabetes (Eaton et al., 1996), independent of other psychiatric disorders and traditional risk factors including age, race, SES, and body mass index (BMI). Furthermore, preliminary evidence suggests that metabolic dysregulation in Type 2 diabetes may improve upon treatment of depression with non-pharmacological therapy (Lustman, Griffith, Freedland, Kissel, & Clouse, 1998). Studies conducted with measures of depressive symptomatology in healthy individuals have been less consistent, with some showing that symptoms predict CHD and clinical coronary events (Dallman, 1993; Grippo & Johnson, 2002; Joynt et al., 2003) as well as incident Type 2 diabetes (Golden et al., 2004; Kawakami et al., 1999), and others failing to find such associations (Saydah, Brancati, Golden, Fradkin, & Harris, 2003; Wulsin, 2004). Evidence seems to be stronger for diagnostic measures of depressive illness, compared to less specific self-report measures of depression which often capture “distress” rather than clinical depression

(Wulsin, 2004). There is some evidence for a graded relationship between depression and coronary disease, such that elevated relative risks for disease have been found for major compared to subclinical depression and depressive symptoms; however, data on the effect of cumulative exposure to depression or depressive symptoms are inconclusive (Rudisch & Nemeroff, 2003).

1.3.2 Depression and Central Adiposity

Further support for a role of depression in the metabolic syndrome comes from studies of the association between depression and central adiposity, one of the putative risk factors for the metabolic syndrome. Findings from the majority of cross-sectional studies conducted with non-clinical populations support a positive association between depressive symptoms and central adiposity in men and women (Ahlberg et al., 2002; Haukkala & Uutela, 2000; Katz et al., 2000; Lee, Kim, Beck, Lee, & Oh, 2005; Petrlova, Rosolova, Hess, Podlipny, & Simon, 2004; Wing et al., 1991), although inconsistent data have been reported (Cota, Vicennati, Ceroni, Morselli-Labate, & Pasquali, 2001; Herva, Laitinen et al., 2006; Marniemi et al., 2002). Three studies have investigated the relationship between depressive symptoms and central adiposity over time; one demonstrated that depressive symptoms predicted increased levels of central adiposity in healthy women, but not men (Nelson et al., 1999), and a second study, conducted with a diabetic sample, showed that depressive symptoms predicted greater WHR in women, and change in depressive symptoms predicted change in WHR in women and men (Lloyd, Wing, & Orchard, 1996). While, the third study, conducted with healthy postmenopausal women, showed that depressive symptoms were cross-sectionally associated with greater WC at baseline and overall depressive symptoms were associated with overall greater WC across time, changes in depression were not associated with changes in WC (Raikkonen, Matthews, & Kuller, 1999).

Results of the majority of cross-sectional studies of clinically depressed young adults showed that depression was associated with greater levels of central adiposity in men and women, (Eskandari et al., 2005; Miller, Freedland, Carney, Stetler, & Banks, 2003), and greater visceral adiposity in women (Kahl et al., 2005; Thakore, Richards, Reznek, Martin, & Dinan, 1997), relative to healthy controls. In contrast, two studies of middle-aged women have failed to show differences in central (Hach, Ruhl, Klotsche,

Klose, & Jacobi, 2006) or visceral adiposity between women with and without major depression (Weber-Hamann et al., 2006), suggesting that the relationship between depression and adiposity may not be consistent across all ages. Interestingly, when depressed patients in the latter study were divided into "normocortisolemic" and "hypercortisolemic" groups, the "normocortisolemic" patients actually exhibited lower visceral fat mass, compared to controls. In the only longitudinal investigation, Weber-Hamann et al. (2006) showed that older men and women diagnosed with a major depressive episode exhibited a marginally greater percent increase in VAT over time as compared to controls, independent of BMI and weight change; however, patients did not have significantly greater mean VAT than controls at baseline or follow-up. It is important to note that all patients in this study underwent six weeks of "standardized" in-patient pharmacological treatment for depression followed by out-patient care; follow-up measures were taken approximately 14 months following in-patient treatment. In aggregate, these studies suggest that depression is cross-sectionally associated with greater levels of central adiposity, particularly in young adults. However, given the potential age differences in the relationship between clinical depression and body fat distribution, as well as the inconsistencies between longitudinal findings with depressive symptoms and clinical depression, further research is needed to clarify the relationship between clinical depression and central adiposity in middle-aged samples and across time.

1.3.3 Depression and Insulin Resistance

Since the mid-1960's researchers have been documenting an association of major depression with aberrant metabolic responsiveness to glucose tolerance (GTT) and insulin tolerance tests (ITT), two indicators of metabolic control. For instance, previous research has shown that patients with major depression exhibit impaired insulin responses during ITTs (Casper, Davis, Pandey, Garver, & Dekirmenjian, 1977; Sachar, Finkelstein, & Hellman, 1971) and GTTs (Mueller, Heninger, & McDonald, 1968). Until recently however, few studies have included healthy controls or other comparison groups, preventing any definitive conclusions about associations between depression and the insulin / glucose system.

Several case-control studies have explored the relationship between clinical depression and proxies for insulin resistance. Using mostly indicators of glucose tolerance or fasting glucose, the majority of studies have shown that patients diagnosed with major depressive disorder exhibit greater metabolic impairment than healthy (Okamura et al., 2000; Weber, Schweiger, Deuschle, & Heuser, 2000; Winokur, Maislin, Phillips, & Amsterdam, 1988; Wright, Jacisin, Radin, & Bell, 1978) or psychiatric controls (Nathan, Sachar, Asnis, Halbreich, & Halpern, 1981); the only study to assess insulin resistance directly showed similar impairment in women with comorbid major depression and borderline personality disorder, compared to psychiatric controls (Kahl et al., 2005). Data on the concurrent association of depressive symptoms with proxies for insulin resistance in healthy samples suggest that depressive symptoms may be associated with indicators of impaired glucose tolerance in White men (Ahlberg et al., 2002; Raikkonen, Keltikangas-Jarvinen, & Hautanen, 1994) but may not be associated with fasting levels in women (Huerta, Mena, Malacara, & Diaz de Leon, 1995). Results of cross-sectional studies that assessed insulin resistance more directly are mixed; one demonstrated an association with depressive symptoms in young adult men (Timonen et al., 2006), although another showed an association in young-adult women but not men (Suarez, 2006). Variation across studies may be attributable, in part, to the specificity and reliability of the assessment of depression and insulin resistance, as well as the use of clinical versus community-based samples. Importantly, the only longitudinal study of depression and insulin resistance showed that depressive symptoms predicted greater insulin resistance in a multi-ethnic sample of women, although this association was mediated by physical activity and central adiposity (Everson-Rose et al., 2004). In aggregate, these studies suggest that depression, especially depressive illness, may be associated with dysregulation of the insulin / glucose system; however, further studies are needed to explore the relationship of depressive illness with specific indicators of insulin resistance and examine this association over time.

1.4 DEPRESSION AND THE METABOLIC SYNDROME

1.4.1 Depressive Symptoms

Two cross-sectional studies have investigated the relationship between depressive symptomatology and the metabolic syndrome. McCaffery, Niaura, Todaro, Swan, and Carmelli (2003) used structural equation modeling to investigate the genetic versus environmental contributions to the covariation of depressive symptoms with the metabolic syndrome in White male monozygotic (MZ) and dizygotic (DZ) twin pairs. Depressive symptoms were assessed by the CES-D, a standardized self-report measure. The metabolic syndrome was represented by the common variance among BMI, WHR, mean arterial pressure (MAP), triglycerides, and glucose. Results showed that depressive symptoms were positively associated with WHR and the overall clustering of metabolic syndrome risk factors. However, the second study failed to find an association between depressive symptoms, assessed by the Hopkins Symptom Checklist-25, and odds of having the metabolic syndrome (defined according to ATP III criteria) in young adult men and women (Herva, Rasanen et al., 2006).

In the only prospective study of depression and the metabolic syndrome, Raikkonen, Matthews, & Kuller (2002) examined the effect of depressive symptomatology and other psychological factors on risk for developing the metabolic syndrome in a sample of 425 pre-, peri-, and post-menopausal women taken from the Healthy Women's Study. Depressive symptoms were assessed using the BDI; the metabolic syndrome was defined according to NHLBI criteria. At baseline, women with the metabolic syndrome had greater levels of depressive symptomatology, supporting a cross-sectional association between depressive symptoms and the metabolic syndrome. Notably, women with higher baseline depression scores had greater risk for developing the metabolic syndrome during the 7.4-year follow-up period, although changes in depression scores were not related to risk for the metabolic syndrome. Presence of the metabolic syndrome did not affect depressive symptoms. There was no effect of health behaviors on any of these relationships, although postmenopausal status was a significant predictor of the metabolic syndrome at baseline.

In aggregate, these studies suggest that depressive symptoms are related to the metabolic syndrome in its entirety, although the data are not entirely consistent. While the findings of Raikkonen et al., (2002) support the notion that depression may be related to pathogenesis of the metabolic syndrome, this study provides no information about depressive illness. Given the preliminary evidence for a graded relationship between depression and disease, as well as evidence for metabolic dysregulation in patients with depressive disorders, a better understanding of the nature of the relationship between clinical depression and the metabolic syndrome is warranted.

1.4.2 Depressive Illness

To our knowledge, only one study has investigated the relationship between depressive illness and the metabolic syndrome, and no study has examined the effect of depression treatment on the metabolic syndrome. In a nationally representative, cross-sectional sample of men and women (NHANES III), aged 17 to 39 years, Kinder et al. (2004) examined the association between lifetime history of major depression and the metabolic syndrome. Lifetime history of depression was treated as a dichotomous variable according to whether or not a participant had a major depressive episode at any point up to and including the time of assessment. The authors found that a history of a depressive episode in women was associated with approximately twice the odds of having the metabolic syndrome as compared to women who had no depression, independent of age, race, education, and health behaviors. This association was not significant in men. Interestingly, post-hoc exploratory analyses showed that neither the number of depressive episodes over one's lifetime, age of first episode, nor the presence of a current episode were significantly associated with the prevalence of the metabolic syndrome. However, it is unclear what cutoff was used to differentiate each of these categories. Although results from this study suggest that clinical depression may be important for understanding the metabolic syndrome, the cross-sectional nature of the study precludes any conclusions about the direction of the association between depressive illness and the metabolic syndrome.

1.5 FACTORS THAT MAY INFLUENCE THE RELATIONSHIP BETWEEN DEPRESSION AND THE METABOLIC SYNDROME

1.5.1 Gender

There is a fairly extensive literature showing that depression is more prevalent in women worldwide (Weissman et al., 1996) and in community samples throughout the United States (Piccinelli & Wilkinson, 2000; Weissman, Livingston, & Leaf, 1991). There is also some evidence to suggest that these differences extend to clinical samples with coronary artery disease (Rudisch & Nemeroff, 2003) and Type 2 diabetes (Musselman et al., 2003). Data from the few studies which examined gender differences in the association between depression and central adiposity are mixed. For example, Nelson et al. (1999) demonstrated that depressive symptoms predicted increased central adiposity 5-7 years later in middle-aged women, but not men. However, Herva, Laitinen, et al. (2006) found that depressive symptoms were associated with greater concurrent central adiposity in men, but not women, and Haukkala and Uutela (2000) found that depressive symptoms were associated with greater central adiposity in men and women. Only one study has examined gender differences in the association with insulin resistance, and results of this study showed that depressive symptoms were positively associated with insulin resistance in women, but not men (Suarez, 2006). Most importantly, the only study to investigate gender differences using the metabolic syndrome in its entirety showed an association with clinical depression in women, but not men (Kinder et al., 2004), suggesting that depression may be a more important predictor for women than men.

1.5.2 Race

Indirect evidence from converging lines of research suggests that race may influence the relationship between depression and the metabolic syndrome. For instance, race differences in visceral adiposity, insulin sensitivity, and incidence and prevalence of Type 2 diabetes are well documented (Davidson, 2001; Perry et al., 2000), and several studies have demonstrated that the relationship between central

adiposity and risk for disease in middle-aged and older women differs between Blacks and Whites (Berman et al., 2001; Dowling & Pi-Sunyer, 1993). There is some evidence to suggest that, compared to Whites, Blacks may be more likely to exhibit comorbid depression and Type 2 diabetes (Blazer, Moody-Ayers, Craft-Morgan, & Burchett, 2002), and depressed Black women may be at greater risk for developing Type 2 diabetes, independent of central adiposity and other risk factors (Everson-Rose et al., 2004). However, the study by Everson-Rose et al. (2004) showed that depressive symptoms predicted greater insulin resistance in Black and White women. No study has explored race differences in the association between depression and central adiposity. To date, only Kinder et al. (2004) have examined race differences in the association between a measure of depression and the metabolic syndrome; they found that the association did not differ between Blacks and Whites. However, further research is needed to explore whether race affects the association between depression and the metabolic syndrome or its core components over time.

1.6 SUMMARY

Evidence from converging lines of research on depression and disease, as well as studies of depression and adiposity or insulin resistance, provide preliminary support for the hypothesis that depression confers increased risk for the metabolic syndrome. Nevertheless, only four studies have directly investigated the relationship between depression and the metabolic syndrome in its entirety. While the results the majority of these studies suggest that depression is associated with the metabolic syndrome, they are limited in several ways. First, three of the studies were cross-sectional, precluding any conclusions about the direction of the association. Although results of the study by Raikkonen et al. (2002) suggest that depressive symptoms precede the metabolic syndrome, prospective studies conducted with diverse samples and measures of depressive illness are needed to better understand the relationship between depression and the metabolic syndrome. Moreover, no study has prospectively explored the effect of behavioral lifestyle factors on the association between depressive illness and the metabolic syndrome.

1.7 PURPOSE OF THE CURRENT STUDY AND HYPOTHESES

The primary purpose of the current study is to investigate the relationship between clinical depression and the metabolic syndrome in a sample of Black and White middle-aged women. To our knowledge, this study will be the first to prospectively examine the association of major depression with the metabolic syndrome. The hypotheses of this study are:

1.7.1 Primary Hypotheses - Metabolic Syndrome

Hypothesis 1: Major depression (lifetime history or current) at baseline will be associated with the presence of the metabolic syndrome at baseline.

Hypothesis 2a: Major depression (lifetime history or current) at baseline will be associated with increased odds of having the metabolic syndrome at any point during the study (baseline - 05).

Hypothesis 2b: Major depression (lifetime history or current) at baseline will be associated with increased odds of having the metabolic syndrome at any point during the five-year follow-up period (visits 01, 03, or 05) in individuals who are free of the metabolic syndrome at baseline.

Hypothesis 3: In participants who are free of the metabolic syndrome at baseline, women with a diagnosis of major depression (lifetime history or current) at baseline will have increased risk for developing the metabolic syndrome across the five-year follow-up period compared to women without a diagnosis of major depression at baseline.

Hypothesis 4: A lifetime history or current diagnosis of major depression (at each visit) will be associated with greater odds of having the metabolic syndrome (at each visit), across the six-year study period.

Hypothesis 5: Predicated associations between depression and the metabolic syndrome will be independent of race, menopausal status, diabetes diagnosis, antidepressant medication use, and other psychiatric diagnoses.

Hypothesis 6: Provided that we confirm an association between depression and the metabolic syndrome, we will explore whether behavioral lifestyle factors (physical activity, smoking, diet) account for this relationship.

1.7.2 Secondary Hypotheses - Central Adiposity and Insulin Resistance

We expect that the association of depression with central adiposity and insulin resistance will follow a similar pattern as Hypotheses 1, 2 and 4. That is, we anticipate that a history of depression will be associated with greater central adiposity and insulin resistance at baseline and across time.

Hypothesis 7: Major depression (lifetime history or current) at baseline will be associated with greater central adiposity and greater insulin resistance at baseline and follow-up visit 05.

Hypothesis 8: A lifetime history or current diagnosis of major depression (at each visit) will be greater central adiposity and insulin resistance (at each visit) across the 6-year study period.

2. METHOD

2.1 STUDY OVERVIEW

The data used in the current study were drawn from a larger study titled “Study of Women’s Health Across the Nation” (SWAN). SWAN is an ongoing, multi-site community based cohort investigation designed to prospectively examine the biological and psychosocial correlates of the menopausal transition, as well as their potential influence on subsequent health and disease risk factors (Sowers et al., 2000). The present investigation focused specifically on data taken from participants in the ancillary Mental Health Study conducted in three of the seven sites of SWAN, in which psychiatric interviews were used to obtain information on lifetime and current psychiatric disorders. Analyses for the current study were based on data collected at baseline and annually thereafter for five additional years, for a total of six visits. Because six-year, prospective psychiatric diagnostic data were available for only one of the three sites (Pittsburgh), this study was limited to data from that site.

2.2 STUDY DESIGN AND SAMPLE

2.2.1 Overview of Parent Study (SWAN) and the ancillary Mental Health Study

The original SWAN study design consisted of an initial, cross-sectional phase (used primarily to identify eligible participants) and a longitudinal cohort study. The sampling procedures and design of the multi-site SWAN parent study have been described previously (Sowers et al., 2000). Participants at the Pittsburgh site were recruited using random digit dialing (RDD) and a voter’s registration list. Eligibility criteria for the longitudinal SWAN study included being aged 42-52, having an intact uterus, having had at least one menstrual period in the previous 3 months, no use of reproductive hormones in the previous 3

months, and self-identifying with one of the site's designated race / ethnic groups, i.e. at Pittsburgh African-Americans or Caucasians. At the Pittsburgh site, a total of 463 women completed the baseline visit for the SWAN parent study. Following the Institutional Review Board's guidelines for human research, written informed consent was obtained at the beginning of the study.

At study entry and annually thereafter as part of the parent investigation, all participants completed a standard assessment protocol, including interviewer-administered and self-administered questionnaires assessing medical, reproductive, and menstrual history; psychosocial factors and physical and psychological symptoms; and behavioral and lifestyle characteristics. Interviewers for the interviewer-administered questionnaires were trained and certified at baseline and annually thereafter. Initial training involved watching a training video, reviewing the interviewer manual and study instruments, and completing an audiotaped interview with a volunteer. This audiotaped interview was subsequently sent to the Coordinating Center, along with a supervisor and self-evaluation form, for evaluation and approval. Annually thereafter, interviewers were required to be recertified via yearly training or evaluation of an audiotaped practice interview.

As part of the parent study, blood was drawn at baseline and bi-annually (visits 01, 03, and 05) for the measurement of lipids and lipoproteins, insulin, and glucose; anthropometric measures (e.g., blood pressure, height, weight, and waist circumference) were taken at baseline and annual follow-up visits. Blood samples for biological markers (i.e., lipids and lipoproteins, insulin, and glucose) were obtained between days two and five of the follicular phase of the menstrual cycle and after a 12 hour fast, ideally before 10:00 am. After completion of the blood draw, all samples were maintained at 4°C until spun and separated, and then frozen at -20° C and shipped on dry ice to the central laboratory (Medical Research Laboratories (MRL), Highland Heights, KY) for analysis (certified by the National Heart Lung and Blood Institute, Centers for Disease Control Lipid Standardization Part III program (Myers, Cooper, Winn, & al., 1989). The interassay coefficients of variation for the blood assay measures were as follows: cholesterol (2.5%), HDL (3.5%), insulin (8.0%), and glucose (2.0%). To ensure accuracy and consistency of sample collection and processing, each phlebotomist or technician was evaluated annually via observation of the following: collection of blood samples; labeling, processing, and storing specimens; shipping procedures;

appropriate use of data collection forms; and site freezer and refrigerator temperatures, back-up systems, and alarm systems.

Quality control procedures for anthropometric and blood pressure measurements included initial technician certification, annual re-certification, on-site monitoring, continuous training and review, and continuous data monitoring. Initial certification involved following a standardized protocol for height, weight, blood pressure, pulse, and waist and hip circumference measurements on two volunteers, followed by identical measurements on the same two volunteers, performed by a certified technician. Differences between measurements conducted by the two technicians could not differ by more than 1 cm for height, waist, and hip circumference; 2 mm Hg for both blood pressure measurements; and 1 kg for weight measurements.

As part of the Mental Health Study, diagnostic psychiatric interviews were conducted at baseline and annually thereafter to determine a lifetime history (baseline only), past year (follow-up visits only), and current psychiatric diagnosis at each visit. Interviews were administered by trained clinical staff (clinicians with an MD or PhD degree, a master's degree in psychology, social work, or a related field, or a degree in psychiatric nursing) within 9 months of the SWAN baseline assessment and again at follow-up visits 01-05 to obtain information on diagnoses that had occurred since the prior study visit. Interviewers completed a multistep certification process which included a training session with a Biometric Institute member, review of videotaped practice interviews by a psychiatric epidemiologist, and review and certification of the videotape by the Biometrics Institute. Interrater reliability scores for lifetime SCID diagnoses (at baseline), assessed in a systematic sample of 12 audiotapes, ranged from good to very good for a variety of psychiatric diagnoses: Kappa = 0.81 for major depressive disorder, 0.78 for substance dependence, and 0.82 for anxiety disorders. Interrater reliability scores for the follow-up visits, assessed using a sample of 49 interviews, were similar: Kappa = 0.88 for major depressive disorder, 0.73 for subsyndromal depression, and 0.83 for anxiety disorders. There were too few cases of substance abuse and dependence at the follow-up visits to reliably determine Kappas for these diagnoses.

Of the 443 women who participated in the Mental Health Study at the Pittsburgh site, 429 provided baseline data for the metabolic syndrome and psychiatric diagnoses. Eight of these women had

a lifetime history of bipolar disorder and / or a manic episode over the 6-year study time-period, and were consequently excluded from the sample. The remaining 421 women were included in the current analyses.

2.3 MEASURES

2.3.1 Psychological Measures

Psychiatric Disorders. Psychiatric diagnoses were assessed annually from baseline (lifetime and current) through year five, for a total of six years. Psychiatric diagnoses, including diagnoses of major and minor depression, were determined by the Structured Clinical Interview for Diagnosis of DSM-IV Axis I Disorders (SCID-IV/NP). The SCID is a semistructured diagnostic interview designed to enable a trained interviewer to establish lifetime and current diagnoses of psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 1994). The SCID has been used with various ethnic groups and its reliability has been demonstrated in numerous studies (Spitzer, Williams, Gibbon, & First, 1992: Williams et al., 1992).

For the purpose of the current study, a lifetime history of depression was defined as the presence of a major depressive episode prior to the SWAN baseline assessment. From this point forward, the term baseline depression" will be used to refer to a lifetime history of a major depressive episode or a current major depressive episode at the baseline visit. Past year depression at each follow-up visit was defined as the presence of a major depressive episode or subthreshold recurrence within the past year; current depression at each visit was defined as the presence of a major depressive episode or subthreshold recurrence currently or within the month preceding that visit. For the purpose of this study, depression at each visit will include a major depressive episode or subthreshold recurrence currently or within the year prior to that visit. The term "cumulative depression" will be used to refer to a major depressive episode at any point up through and including the current visit. Table 1 presents the number of participants at baseline and each follow-up visit who met criteria for a major depressive episode or subthreshold recurrence, as well as those who met criteria for any type of depressive episode (i.e., major depressive episode, subthreshold recurrence, minor depressive episode, dysthymia). As seen in Table 1,

Table 1: Sample characteristics at baseline and follow-up visits

Number of participants in final sample	421		
Number in original sample	443		
Number with complete data at visit 00	429		
Number with bipolar disorder or manic episode	8		
Age Range (years)	42-52 (M = 45.6 ± 2.5)		
Self-Identified Ethnicity	277 White / Caucasian 144 Black / African-American		
Education (years)	M = 15, SD = 2.2		
Menopausal Status	Pre / early peri	Late peri	Post / surgical
Visit 00 (n = 418)	418 (99.3%)	0	0
Visit 01 (n = 384)	330 (85.9%)	15 (3.9%)	7 (1.8%)
Visit 02 (n = 371)	276 (74.4%)	26 (7.0%)	19 (5.1%)
Visit 03 (n = 373)	231 (61.9%)	29 (7.8%)	54 (14.5%)
Visit 04 (n = 364)	182 (50.0%)	39 (10.7%)	86 (23.6%)
Visit 05 (n = 340)	136 (40.0%)	43 (12.6%)	122 (35.9%)
Depression	Major or Subthreshold Recurrence		Major, Minor, or Dysthymia
Lifetime history / current at 00	150 (35.6%)		212 (50.4%)
Visit 00 past year / current only (n=415)	48 (11.6%)		N/A [2]
Visit 01 (n = 384)	52 (13.5%)		68 (24.0%)
Visit 02 (n = 386)	52 (13.5%)		65 (16.8%)
Visit 03 (n = 377)	47 (12.5%)		60 (14.3%)
Visit 04 (n = 364)	44 (10.5%)		53 (12.6%)
Visit 05 (n = 353)	48 (11.4%)		56 (13.3%)
Lifetime history / current anxiety disorder at visit 00 (n=421)	101 (24%)		
Lifetime history / current alcohol at visit 00 (n=420)	54 (12.9 %)		
Lifetime history / current drug at visit 00 (n = 421)	35 (8.3%)		
Antidepressant Use (baseline n = 421)			
Lifetime history / current at visit 00 [3]	64 (15.2%)		
Visit 01 (n = 384)	75 (19.5%)		
Visit 02 (n = 386)	69 (17.9%)		
Visit 03 (n = 377)	67 (17.8%)		
Visit 04 (n = 364)	73 (20.1%)		
Visit 05 (n = 353)	83 (23.5%)		

Note: [1] M = mean, SD = standard deviation; [2] Data for last occurrence of minor depression and dysthymia not available; [3] A total of 64 participants had a lifetime history of antidepressant use, 33 of whom reported current antidepressant use at baseline.

approximately 35% of the sample met criteria for a lifetime history or current diagnosis of major depression at baseline, and approximately 50% of the sample met criteria for major depression, minor depression, or dysthymia at baseline.

Other psychiatric data included any history of an Axis I anxiety disorder (including panic disorder, social phobia, specific phobia, agoraphobia, obsessive-compulsive disorder, or generalized anxiety disorder), and any history of alcohol or substance abuse or dependence (see Table 1).

Antidepressant Use. Data on lifetime history of antidepressant use, as well as past year and current use at each visit, were collected annually during the SCID interview (see Table 1). For the purpose of the current investigation, baseline antidepressants will refer to a lifetime history of

2.3.2 Self-Administered and Interviewer-Administered Questionnaires

Sociodemographic and Descriptive Variables

Ethnicity was self-identified as African-American or Caucasian; 34% of study participants identified themselves as Black / African-American. Education was measured continuously as the highest grade level. At baseline, menopausal status was categorized according to bleeding patterns, defined as premenopausal (no decrease in predictability of menses onset in prior 12 months) or early perimenopausal (menstrual period in the past three months, but less predictable periods in the last 12 months). For the purpose of the current study, menopausal status at each of the follow-up visits was coded as one of the following four categories: premenopausal (menstrual period within past 3 months and no change in regularity) or early perimenopausal (menstrual period within past 3 months but self-reported change in regularity); late perimenopausal (menstrual period within the past year but not in the past 3 months); postmenopausal (hysterectomy, oopherectomy, or no bleeding in the 12 months prior to the interview for that visit); or unknown due to HRT use (see Table 1 for a summary of sample characteristics).

Health Behaviors

Table 2 presents the frequencies and distributions for the health behaviors and select biological variables at baseline and subsequent follow-up visits.

Table 2: Frequencies and distributions of health behaviors and biological variables

Variable	N (%) [1]		
Smoking			
Visit 00 (n = 418)		78 (18.7%)	
Visit 01 (n = 384)		63 (16.4%)	
Visit 02 (n = 366)		61 (16.7%)	
Visit 03 (n = 363)		54 (14.9%)	
Visit 04 (n = 358)		55 (15.4%)	
Visit 05 (n = 338)		47 (13.9%)	
Physical Activity (Visit 00 only)	M = 8.0	SD = 1.7	Skew = 0.06
Total kcal (Visit 00 only)	M = 1899.6	SD = 761.9	Skew = 1.39
% kcal from fat (Visit 00 only)	M = 33.8	SD = 7.4	Skew = 0.27
% kcal from carb (Visit 00 only)	M = 51.0	SD = 8.3	Skew = 0.11
Metabolic Syndrome (MS)		Present	
Visit 00 (n = 421)		85 (20.2%)	
Visit 01 (n = 365)		82 (22.5%)	
Visit 03 (n = 322)		72 (22.4%)	
Visit 05 (n = 286)		60 (21.0%)	
Ever from 00-05 (n = 324) [2]	123 (38% of women with available data; 29% of original sample)		
Incident through 05	38 (9% of original sample; 11.3% of women free of MS at baseline)		
Waist Circumference (cm)			
Visit 00 (n = 415)	M = 87.9	SD = 15.2	Skew = 0.88
Visit 01 (n = 379)	M = 88.7	SD = 15.6	Skew = 0.88
Visit 02 (n = 353)	M = 89.8	SD = 15.4	Skew = 0.89
Visit 03 (n = 337)	M = 89.9	SD = 15.7	Skew = 1.0
Visit 04 (n = 325)	M = 90.3	SD = 15.1	Skew = 0.75
Visit 05 (n = 313)	M = 89.9	SD = 15.6	Skew = 0.81
HOMA-IR [3]			
Visit 00 (n = 412)	M = 2.8	SD = 3.8	Skew = 6.8
Visit 01 (n = 357)	M = 3.0	SD = 4.7	Skew = 8.7
Visit 03 (n = 319)	M = 3.1	SD = 5.2	Skew = 9.9
Visit 05 (n = 269)	M = 3.0	SD = 4.7	Skew = 7.7
BMI (kg/m^2) at Visit 00 (n = 416)	M = 28.7, SD = 6.4		
Diabetes (fasting glucose $\geq$ 126 mg/dl or taking medication for diabetes)		Present	
Visit 00 (n = 417)		25 (6.0%)	
Visit 01 (n = 361)		25 (6.9%)	
Visit 03 (n = 321)		18 (5.6%)	
Visit 05 (n = 283)		20 (7.1%)	
Ever from 00-05 (n = 283)		25 (8.8%)	

Note: [1] M = mean, SD = standard deviation [2] If missing and didn't develop metabolic syndrome, counted as missing. [3] HOMA-IR values for all visits were transformed using square-root transformations.

Smoking status. Cigarette smoking was determined at all visits by asking women to respond to three items on the amount smoked and quit date, if applicable. At each visit (baseline – 05), a dichotomous smoking variable (yes/no) was created to indicate current smoking status.

Diet. Diet was assessed at baseline using a modification of the Block food frequency questionnaire (FFQ) (Block et al., 1986; Block, Thompson, Hartman, Larkin, & Guire, 1992), described in detail elsewhere (Huang et al., 2002). The interview-administered questionnaire included 103 items covering the majority of foods that are nutrient contributors to the diets of the ethnic groups in SWAN. The interview yielded a variety of scores; this study focused on total kilocalories (including alcohol) and percent kilocalories from fat and carbohydrates.

Physical Activity. Physical activity was measured at baseline using a self-administered questionnaire based on the Baecke physical activity questionnaire (Baecke, Burema, & Fritijers, 1982). Responses to a series of questions on typical physical activity in the past year were used to create three distinct physical activity indices corresponding to three domains (based on the frequency, intensity, and duration of the following activities: sports and exercise, active living, and household / caregiving); possible scores for each index range from 1-5. A continuous measure of total activity was then created by summing these three indices.

2.3.3 Biological Measures

Waist circumference and blood pressure were measured at baseline through follow-up visit 05. Triglycerides, high-density lipoprotein cholesterol (HDL-C), insulin, and glucose were assessed at baseline and follow-up visits 01, 03, and 05. Because data for some of the components of the metabolic syndrome were not collected at all time points, data for the metabolic syndrome were available for a total of four time points (baseline, 01, 03, and 05).

Metabolic Syndrome. For the current study, a participant was classified as having the metabolic syndrome if she met three or more of the following criteria:

1) Abdominal Obesity: Waist circumference >88cm.

2) Hypertriglyceridemia: Triglyceride value > 150 mg/dl.

3) Low HDL cholesterol: HDL value < 50 mg/dl.

4) Hypertension: SBP > 130 or DBP > 85 mmHg or taking “blood pressure pills”.

5) Impaired fasting glucose: fasting glucose > 110 mg/dl (or having ever been classified as diabetic)

A variable was then created for each visit to indicate whether, using the criteria above, a participant has the metabolic syndrome at that visit, irrespective of her metabolic syndrome classification at all previous visits. A “cumulative index” of the metabolic syndrome was also created to indicate whether a participant had the metabolic syndrome at any point during the study period (baseline – visit 05). A participant’s cumulative metabolic syndrome status was coded as “present” if she had the metabolic syndrome at the current or any previous visit; status was coded as “absent” if she did not meet criteria at the current or any previous visit; status was coded as missing if she had missing data at the current or any previous visit and no current or previous diagnosis of the metabolic syndrome. As seen in Table 2, approximately 20% of the women were classified as having the metabolic syndrome at baseline; 29% of the women were classified as ever having had the metabolic syndrome (cumulative index) over the course of the study.

Central Adiposity. Waist circumference (cm) was used as the index of central adiposity. Waist circumference (WC) was measured at the level of the natural waist, defined as the narrowest part of the torso as seen from the anterior aspect. In cases where a waist narrowing was difficult to identify, the measure was taken at the smallest horizontal circumference in the area between the ribs and the iliac crest. The mean WC for this sample at baseline was 87.9cm (SD = 15.2; see Table 2).

Triglycerides / HDL Cholesterol. All lipid, lipoprotein and apolipoprotein fractions were analyzed on EDTA-treated plasma (Steiner, Frieidel, Bremner, & Stein, 1981; Warnick & Albers, 1978). Total cholesterol and triglycerides were analyzed by enzymatic methods on a Hitachi 747 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN) as previously described (Steiner et al., 1981), and HDL-C was isolated using heparin-2M manganese chloride (Warnick & Albers, 1978).

Blood Pressure. Blood pressure was measured according to a standardized protocol, with readings taken on the right arm, with the respondent seated and feet flat on the floor for at least 5 minutes prior to the measurement. Respondents had not smoked or consumed any caffeinated beverage within

30 minutes of blood pressure measurement. Appropriate cuff size was determined based on arm circumference. A standard mercury sphygmomanometer was used to record systolic (SBP) and diastolic (DBP) pressures at the first and fifth phase Korotkoff sounds. Two sequential blood pressure values were completed, with a minimum two-minute rest period between measures.

Insulin and Glucose. Insulin and glucose were measured from the blood specimens obtained after a 12-hour fast and drawn during days 2-5 of the follicular phase of the menstrual cycle. Serum insulin was measured using radioimmunoassay (RIA) (DPC Coat-A-Count, Los Angeles, CA) procedure and monitored as part of the monthly quality assurance program provided by the Diabetes Diagnostic Laboratory at the University of Missouri. Glucose was measured using a hexokinase-coupled reaction on a Hitachi 747-200 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN).

Insulin Resistance. Insulin resistance was calculated using the revised Homeostasis Model Assessment (HOMA-IR) equation (Wallace, Levy, & Matthews, 2004). The HOMA-IR is considered an acceptable surrogate measure of insulin resistance for use in studies in which more invasive measures of insulin resistance are unfeasible or excessive (Bonora et al., 2000; Wallace & Matthews, 2002). It is based on fasting plasma glucose and insulin concentrations and is derived from a computer algorithm, it accounts for variations in hepatic and peripheral glucose resistance, and it is calibrated to insulin assays that are currently available. Greater HOMA-IR values indicate decreased insulin sensitivity or insulin resistance; the mean HOMA-IR value at baseline was 2.8 (SD = 3.8; see Table 2).

Body Mass Index. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Height was measured without shoes using a fixed stadiometer. Weight was measured without shoes, and in light indoor clothing, using a either a digital or balance beam scale; scales were calibrated monthly. The mean BMI at baseline was 28.7 kg/m^2 (SD = 6.4; see Table 2).

Diabetes. Diabetes was ascertained at baseline and visits 01, 03, and 05; a woman was classified as having diabetes at that visit if she reported taking “insulin or pills for sugar in her blood” or had a fasting glucose level > 126 mg/dl. At baseline, 25 women met these criteria for diabetes, 18 of whom reported taking “insulin or pills for sugar in her blood”.

2.4 DETAILED HYPOTHESES AND ANALYTIC PLAN

2.4.1 Data Management and Statistical Software

All data from the SWAN parent study (i.e., physical measures, biological assays, health behaviors, sociodemographic and descriptive variables) were centrally stored at the SWAN Coordinating Center, located at the University of Pittsburgh. Data for biological assays were sent electronically from the SWAN core laboratory (MRL) after completion of specimen analysis and results were entered into an oracle database followed by conversion for use in SAS. Data for all other physical measures, health behaviors, sociodemographic and descriptive variables were entered into an oracle database at the Coordinating Center and converted for use in SAS. The data management system at the Coordinating Center automatically checks for missing data and violated validation ranges each time a form is entered. An edit report is generated each time possible errors are detected, and completed reports are reviewed to correct the error or confirm the accuracy of the data.

All psychiatric data collected during the SCID interviews were recorded and coded in the SCID booklet by the interviewer who reviewed it for accuracy and consistency with diagnoses. Final diagnoses were coded on SCID Summary Score Sheets (SSS). The interviewer transferred all data that were not diagnoses (e.g., medication use) onto custom designed SCID Data Entry Forms (DEF). A research associate conducted a visual review of the SSS/DEF to check for inconsistencies and then documented them in a Manual Edit Report; inconsistencies were resolved by the interviewer prior to data entry. Two computers equipped with the data entry software were used for entry, verification, logic and range checks, and editing of SCID data. The SCID data were stored on a local network drive for use by SWAN personnel only; data were backed up on a daily basis.

Data for the current analyses were obtained from the Coordinating Center (parent study data) or the local network drive (SCID data) and subsequently merged and converted for use in SPSS and Stata Statistical Software (Stata Corporation, College Station, Texas; release 9.0).

2.4.2 Data Reduction and Preliminary Analyses

Preliminary analyses were conducted to examine the distribution of all continuous variables (see Table 2); highly skewed variables were transformed as indicated. Inter-correlations among baseline covariates, depression (lifetime history / current at baseline), and the metabolic syndrome (baseline and cumulative through visit 05) were calculated using Pearson's r (continuous variables), point-biserial (continuous and dichotomous), and Phi-correlation (dichotomous) coefficients.

Preliminary analyses were also conducted to examine and compare the characteristics of participants with a baseline diagnosis of lifetime history / current major depression; minor depression or dysthymia (lifetime history / current); and no depression. While it was originally proposed to define depression as the occurrence of any type of depression (major, minor, dysthymia) to increase the power for the proposed analyses, preliminary analyses showed that mean waist circumference, prevalence of the metabolic syndrome, and prevalence of a major depressive episode across time did not differ between women with a history or current diagnosis of minor depression or dysthymia at baseline and women with no depression. Moreover, it appeared that women with a lifetime history or current diagnosis of major depression at baseline had a greater prevalence of the metabolic syndrome at baseline and the follow-up visits, and they also had a greater number of major depressive episodes (or subthreshold recurrences) at each of the follow-up visits, suggesting that it would be inappropriate to combine all women with any depression diagnosis (see Table 1 in Appendix A for percentages). To be thorough, analyses for Hypotheses 1 and 2 were conducted with depression defined both as major depression only and as any depression (major, minor, dysthymia). Consistent with the preliminary sample comparisons, the addition of minor depression and dysthymia weakened the association between depression and the metabolic syndrome (see Tables 2 and 3 in Appendix A for results). Hence, the decision was made to define depression as the occurrence of a major depressive episode or subthreshold recurrence only; all further analyses were conducted with depression defined in this manner, and depression hereafter will refer to major depression / subthreshold recurrence only.

2.4.3 Primary Hypotheses - Metabolic Syndrome

Hypothesis 1: Major depression (lifetime history or current) at baseline will be associated with the presence of the metabolic syndrome at baseline. In comparison to subjects with no lifetime history or current diagnosis of major depression at baseline, subjects with major depression were expected to have greater frequency of the metabolic syndrome at baseline (Figure 2). Chi-square tests were conducted to examine the association of baseline depression (dichotomous) with presence of the metabolic syndrome (dichotomous) at baseline.

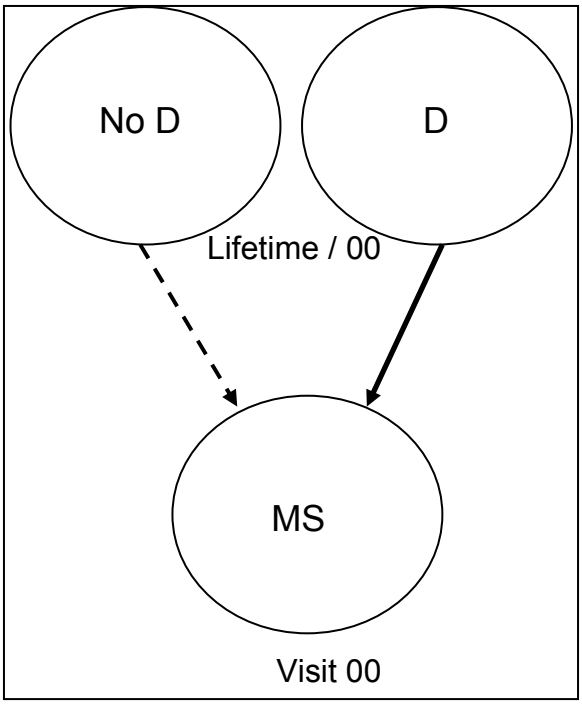

Figure 2: Hypothesis 1: Baseline association between lifetime history / current depression and the metabolic syndrome
Note: No D = No major depression; D = Major depression

Hypothesis 2a: Major depression (lifetime history or current) at baseline will be associated with increased odds of having the metabolic syndrome at any point during the study (baseline - 05) (Figure 3a). A series of stepwise logistic regression analyses were used to examine the odds of having the metabolic syndrome during any visit ("cumulative index" of the metabolic syndrome at visit 05) based

on baseline depression (dichotomous). In the first set of analyses, depression was entered on step 1 and baseline age and race on step 2. In all further analyses, depression, race, and baseline age were entered on step 1, followed by the planned covariates that showed a significant univariate correlation (p < .10) with baseline depression or the metabolic syndrome (baseline or cumulative through 05).

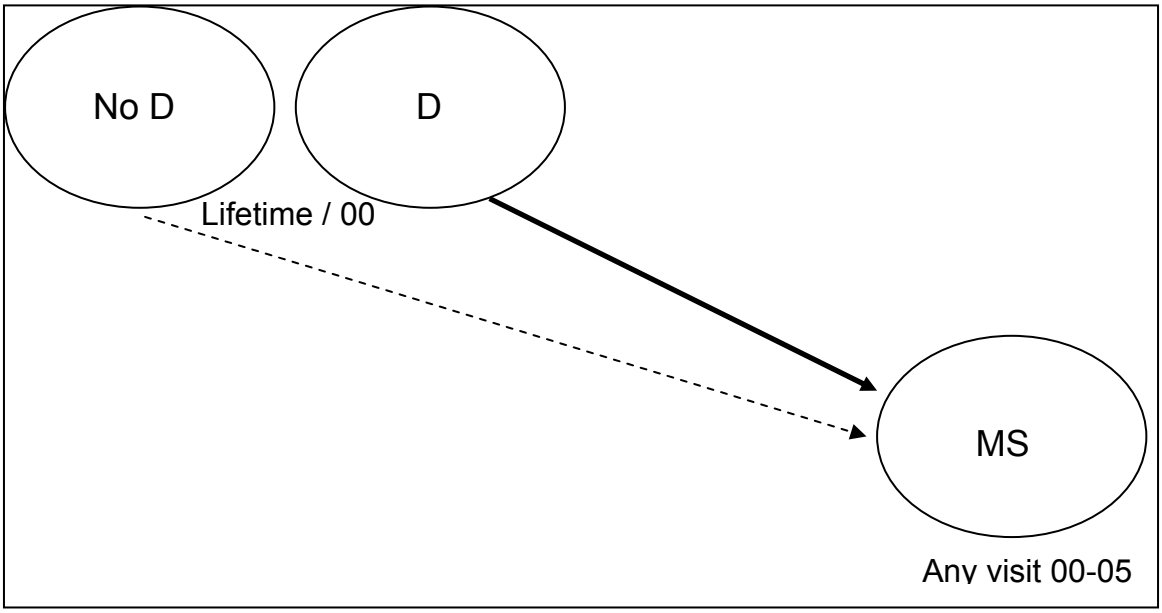

Figure 3a: Hypothesis 2a: Association between lifetime history / current depression at baseline and cumulative index of the metabolic syndrome through visit 05
Note: No D = No major depression; D = Major depression; MS = Metabolic syndrome

Hypothesis 2b: Major depression (lifetime history or current) at baseline will be associated with increased odds of developing the metabolic syndrome at any point during the 5-year follow-up period (visits 01, 03, or 05) in individuals who are free of the metabolic syndrome at baseline (Figure 3b). Analyses paralleled those described in hypothesis 2a, except the sample was limited to those women who were free of the metabolic syndrome at baseline.

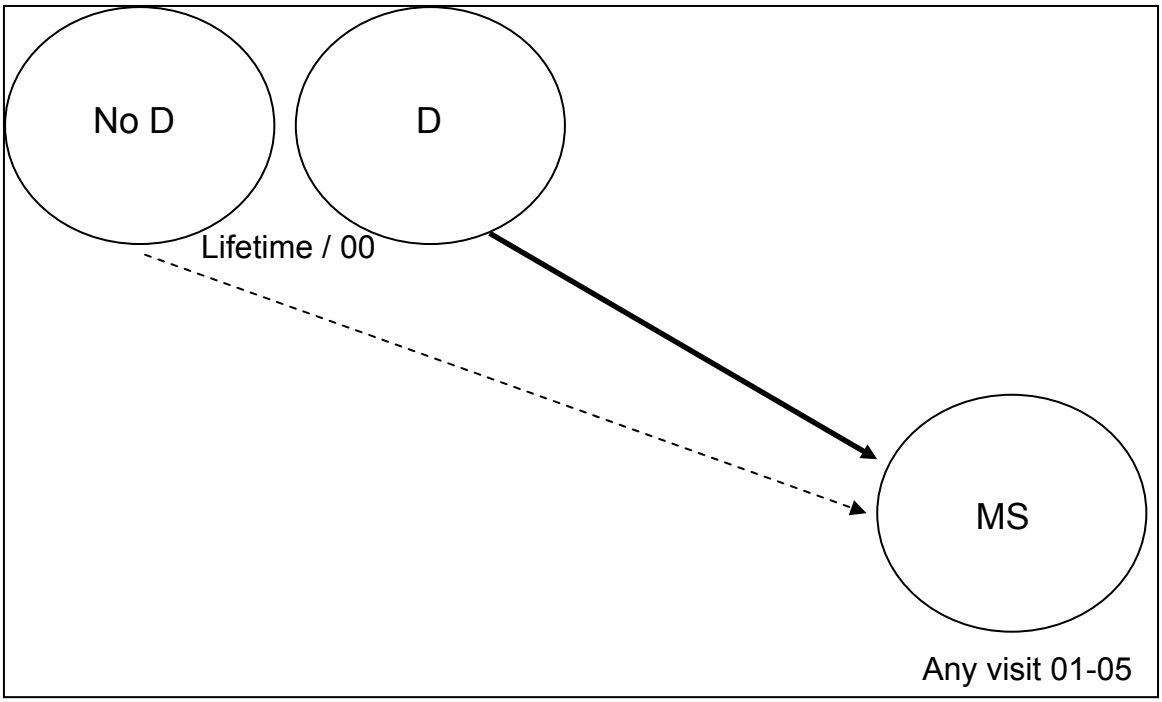

Figure 3b: Hypothesis 2b: Association between lifetime history / current depression at baseline and incident metabolic syndrome during follow-up visits
Note: No D = No major depression; D = Major depression; MS = Metabolic syndrome

Hypothesis 3: In participants who are free of the metabolic syndrome at baseline, women with a diagnosis of major depression (lifetime history or current) at baseline will have increased risk for developing the metabolic syndrome across the five-year follow-up period compared to women without a diagnosis of major depression at baseline (Figure 4). In participants who were free of the metabolic syndrome at baseline, unadjusted and adjusted Cox proportional hazards models were used to calculate risk of developing the metabolic syndrome across the follow-up visits based on baseline depression diagnosis (lifetime history / current; dichotomous). This analytic procedure accounts for missing data, censoring, and unequal follow-up time; it allows for continuous and categorical covariates; and it allows for comparisons between groups without making assumptions about the underlying distribution of the hazard function (Cleves, Gould, & Gutierrez, 2004).

Univariate analyses were first conducted with baseline depressive status in the model, followed by multivariate analyses adjusting for baseline age and race. Baseline menopausal status was entered as a covariate to initial models to confirm that associations were independent of menopausal status. Covariates for fully adjusted models were chosen based on results of preliminary correlational analyses;

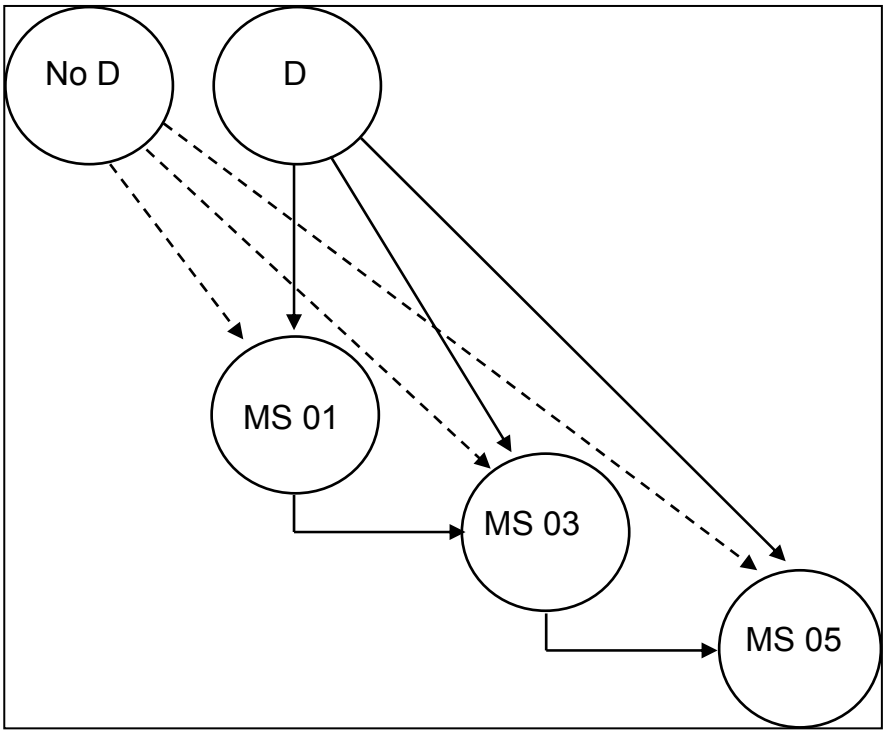

Figure 4: Hypothesis 3: Cox proportional hazard model of the effect of baseline depression on risk of developing the metabolic syndrome at a follow-up visit
Note: No D = No major depression; D = Major depression; MS = Metabolic syndrome

all planned covariates which were related to depression (baseline) or the metabolic syndrome (baseline or cumulative index at 05) at the $p < .10$ level were entered into the models. Visit year was used as the unit of analysis, and the incident (failure) date was defined as the year of the follow-up visit during which the participant was first classified as having the metabolic syndrome. The proportional hazards assumption was evaluated and confirmed via a test for zero-slope of Schoenfeld residuals, indicating that the log hazard ratio function is constant over time (Schoenfeld, 1982).

Hypothesis 4: A lifetime history or current diagnosis of major depression or subthreshold recurrence across time will be associated with increased odds of having the metabolic syndrome across the 6-year study period. The relationship between depression and the metabolic syndrome across time was examined using Generalized Estimating Equations (GEE). GEE is a type of general linear model (GLM) used for clustered data which adjusts for the within-subject correlation present among repeated observations over time (Liang & Zeger, 1986; Zeger, Liang, & Albert, 1988). Unlike many other methods used to analyzed repeated measures data (e.g. repeated measures ANOVAs), GEE can handle

longitudinal data on subjects with observations that are varying in number and are unequally spaced. This method is suitable for the longitudinal analysis of both dichotomous and continuous covariates and outcomes, and it allows for time-varying independent and dependent variables. This modeling technique tests the association between a diagnosis of depression and the presence of the metabolic syndrome at each visit, and subsequently collapses across visits. More specifically, coefficients are calculated through a series of logistic regression models at each time-point, corrected for the correlation among time points, and then subsequently collapsed across all time-points to generate a final coefficient. The final regression coefficient represents an average of the "between-subjects" effects (comparing women with depression to women with no depression) and "within-subjects" effects (comparing the effect when a woman is depressed to the effect when that woman is not depressed).

To test the hypothesis that depression (at visits 00, 01, 03, and 05) was associated with greater odds of having the metabolic syndrome (at visits 00, 01, 03, and 05; Figure 5a), a GEE model was estimated with a binomial outcome (presence / absence of metabolic syndrome) distribution and a logit link. The link function specifies a nonlinear transformation of the predicted values and is used to model responses when the relationship between the independent and dependent variables is thought to be nonlinear (Hardin & Hilbe, 2003). Based on preliminary examination of correlations between repeated measurements, an exchangeable working correlation structure (assumes that the correlations between subsequent measurements are similar, irrespective of the length of the time interval) was adopted to account for the correlation among repeated observations. The GEE model produces an odds ratio and 95% confidence interval for the metabolic syndrome based on major depression diagnosis (yes / no), controlling for age at each visit, accounting for the effects of time. For these analyses, depression and age were treated as time-varying independent variables (IV), and the metabolic syndrome was treated as a time-varying dependent variable (DV). An interaction between depression and age was also entered into the model to examine whether the odds of having the metabolic syndrome with age were greater for participants with depression.

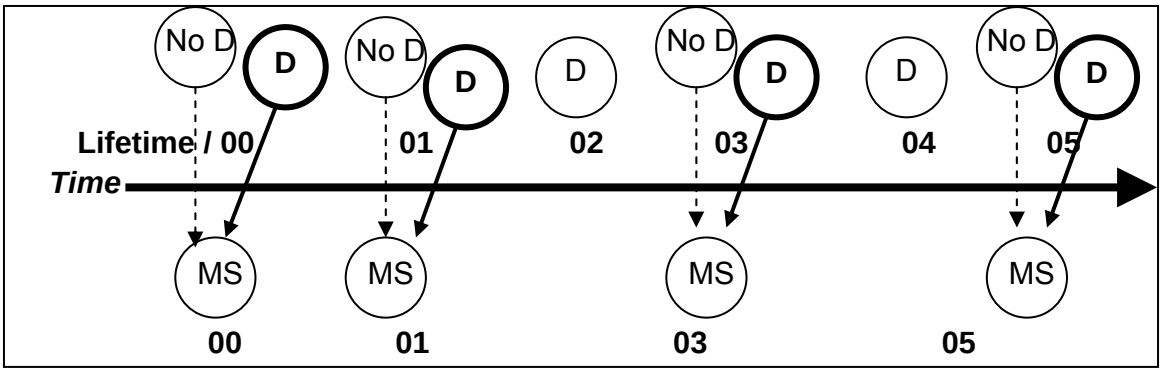

Figure 5a: Hypothesis 4: GEE model of associations between depression and the metabolic syndrome across time
Note: No D = No major depression or subthreshold recurrence at that visit; D = Major depression or subthreshold recurrence at that visit; MS = Metabolic syndrome

A second, "time-lag" model was produced to test the hypothesis that depression precedes the metabolic syndrome by estimating the odds of having the metabolic syndrome (dichotomous) at time t_x, based on a cumulative index of depression at time t_{x-1} (presence / absence of a major depressive episode at any point up to and including that visit; see Figure 5b), controlling for time and age at each visit (concurrent with the metabolic syndrome). This model estimates an odds ratio and 95% confidence interval showing the association between a cumulative index of a prior major depressive episode (at any point up to and including the previous visit; for lifetime, visit 00, 02, and 04) and the presence of the metabolic syndrome at the current visit for each visit (visits 00, 01, 03, and 05), and subsequently collapses across visits to generate the final coefficient. For this model, depression was treated as a type of time-varying DV, in that women were allowed to move from "not depressed" to "depressed"; however, once classified as depressed, they stayed in this category for the remainder of the visits. As with the previous model, age was treated as a time-varying IV, and the metabolic syndrome was treated as a time-varying DV. Finally, as previously described, this model was estimated with a binomial outcome distribution (presence / absence of metabolic syndrome), and an exchangeable correlation structure was adopted to account for the correlation among repeated observations.

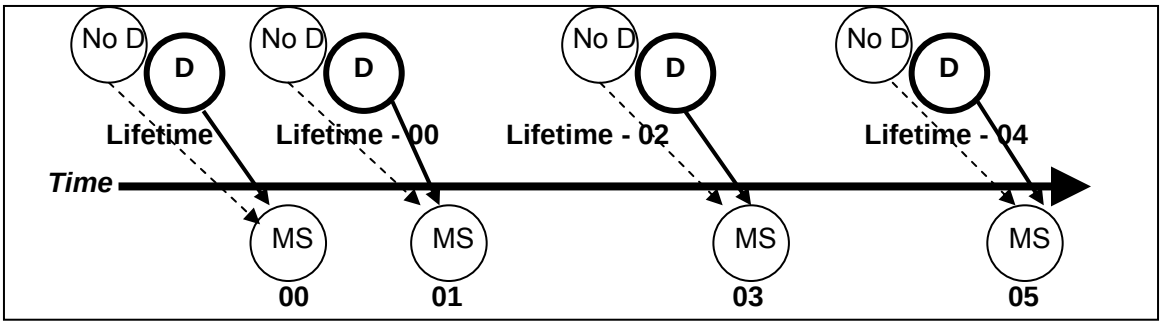

Figure 5b. Hypothesis 4b: GEE time-lag model of associations between cumulative depression at the previous visit and the metabolic syndrome at the following visit across time
Note: No D = No major depression or subthreshold recurrence up through and including the visit; D = Major depression or subthreshold recurrence up through and including the visit; MS = metabolic syndrome

2.4.4 Exploratory Analyses

Hypothesis 5: Predicated associations between depression and the metabolic syndrome will be independent of race, menopausal status, diabetes diagnosis, antidepressant medication use, and other psychiatric diagnoses. As described above, race was entered into models 2-4 to examine whether the association between depression and the metabolic syndrome was reduced; menopausal status (baseline for models 2 and 3; at each visit for model 4) was entered into the same models to confirm that the associations were independent of menopausal status. Analytically, categories of menopausal status were compared to premenopause. Analyses were rerun excluding participants with diabetes at baseline (n = 25) to confirm that the associations were independent of diabetes.[1]

Chi-square tests were used to test for differences between individuals with and without depression (lifetime history / current diagnosis) on baseline diagnoses of anxiety, drug, and alcohol use disorders (all lifetime history / current) and baseline antidepressant use (lifetime history / current use). Variables that differed significantly between the two groups ($p < .10$) were added to examine their influence on the association between depression and the metabolic syndrome.

Hypothesis 6: Health behaviors (physical activity, diet, and smoking) will be added to significant models to explore whether the association between depression and the metabolic syndrome is reduced. Preliminary analyses were conducted to explore the association of physical activity, total caloric intake, percent calories from fat, percent calories from carbohydrates, and smoking

(baseline only) with baseline depression (lifetime history / current) and the metabolic syndrome (baseline and cumulative through visit 05). Variables which were correlated with depression or the metabolic syndrome at the $p < .10$ level were entered into the models to examine whether the association between major depression and the metabolic syndrome was reduced.

2.4.5 Secondary Hypotheses - Central Adiposity and Insulin Resistance

Hypothesis 7: Major depression (lifetime history or current) at baseline will be associated with increased central adiposity and increased insulin resistance at baseline and follow-up visit 05. Univariate and multivariate (controlling for baseline age and race) General Linear Model (GLM) ANOVAs were used to test for significant differences between depression groups at baseline (dichotomous) in mean WC and HOMA values at baseline and visit 05 (Figures 6 and 7).

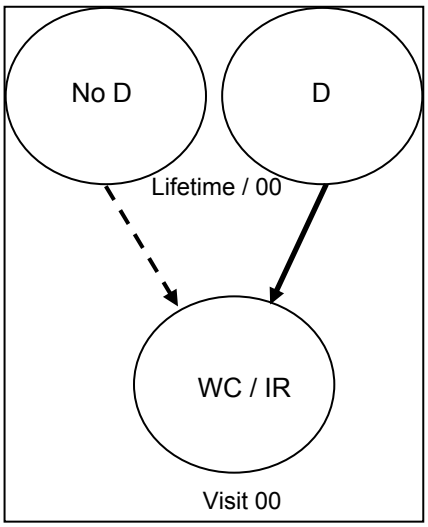

Figure 6: Hypothesis 7: Baseline associations between lifetime history / current depression and waist circumference or insulin resistance
Note: No D = No major depression
D = Major depression;
WC = waist circumference; IR = insulin resistance

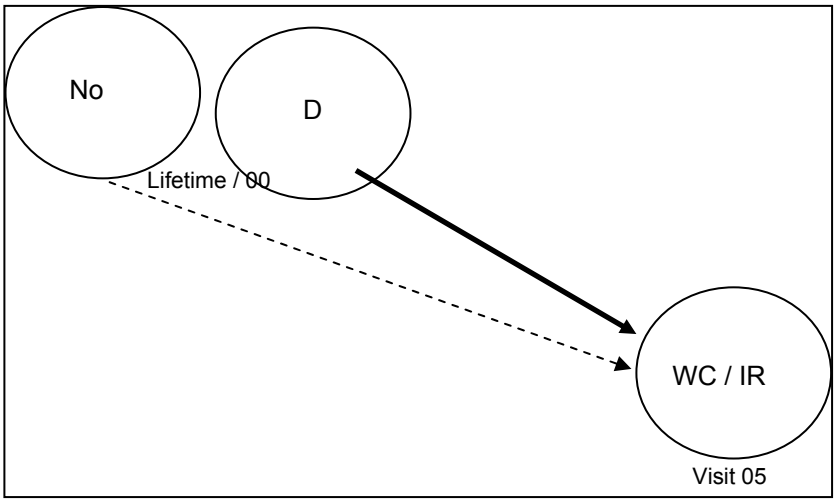

Figure 7. Hypothesis 7: Association between lifetime history / current depression at baseline and waist circumference or insulin resistance at visit 05
Note: No D = No major depression; D = Major depression; WC = waist circumference; IR = insulin resistance

Hypothesis 8: Based on the results of the above GLMs, significant group differences in mean waist circumference will be present throughout the study, such that depression (major depression or subthreshold recurrence) will be associated with higher waist circumference across time. GEE was used to examine associations between depression (at each visit) and WC (at each visit) across the study period. Waist circumference was treated as a continuous variable. The GEE model was estimated with a Gaussian (normal) outcome distribution and an identity link; an exchangeable correlation structure was adopted to model the correlation among repeated observations. The first model tested the hypothesis that depression (at each visit) is associated with greater WC (at each visit) across time (see Figure 8a). For these analyses, depression and age were treated as time-varying independent variables (IV), and waist circumference was treated as a time-varying dependent variable (DV). An interaction between depression and age was also entered into the model to examine whether changes in waist circumference with age were greater for participants with depression. As with Hypothesis 4, this modeling technique tests the association between a diagnosis of depression and waist circumference at each visit by calculating unstandardized coefficients through a series of linear regression models at each time-point, corrected for the correlation among time points, and then subsequently collapsed across all time-points to

generate a final showing the magnitude of the relationship between major depression (dichotomous) and WC, controlling for age at each visit.

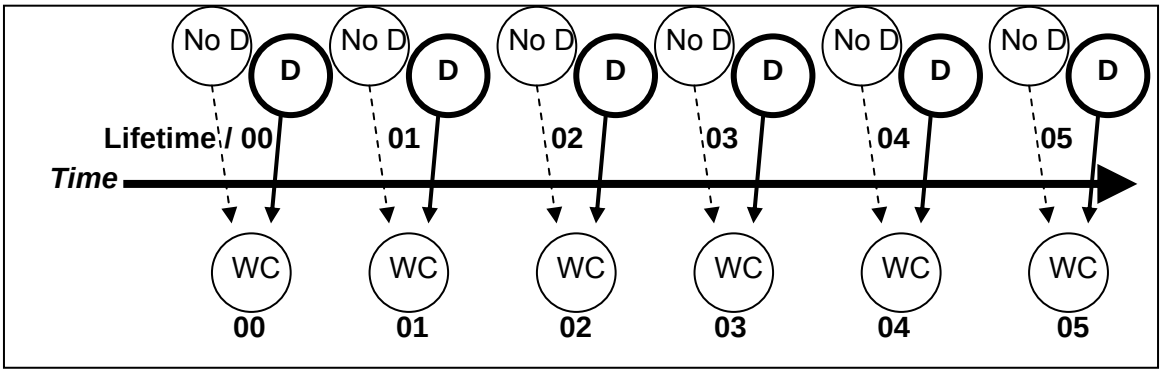

Figure 8a: Hypothesis 8a: GEE model of associations between depression and waist circumference across time.
Note: No D = No major depression or subthreshold recurrence at that visit; D = Major depression or subthreshold recurrence at that visit; WC = Waist circumference

A second, "time-lag" model was produced to test the hypothesis that depression precedes increased WC by examining associations between a cumulative index of depression at time t_{x-1} (presence / absence of a major depressive episode at any point up to and including that visit) and WC at time t_x, controlling for age at each visit (concurrent with WC; see Figure 8b). This model estimated unstandardized regression coefficients showing the magnitude of the longitudinal relationship between any prior major depressive episode (up to and including the visit; for lifetime, and visits 00 – visit 04) and WC at the current visit (visits 00 – 05), and subsequently collapses across visits to generate the final coefficient (see Figure 8b). For this model, depression was treated as a type of time-varying DV, in that women were allowed to move from "not depressed" to "depressed"; however, once classified as depressed, they stayed in this category for the remainder of the visits. As with the previous model, age was treated as a time-varying IV, and waist circumference was treated as a time-varying DV. As with the model described above, this model was estimated with a Gaussian (normal) outcome distribution and an identity link. An exchangeable correlation structure was adopted to account for the correlation among repeated observations.

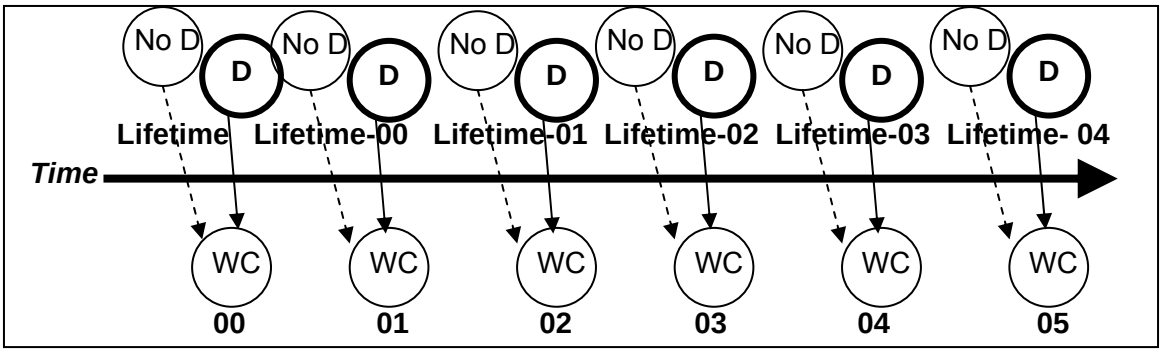

Figure 8b: Hypothesis 8b: GEE time-lag model of associations between cumulative depression at the previous visit and waist circumference at the following visit across time
Note: No D = No major depression or subthreshold recurrence up through and including the visit; D = Major depression or subthreshold recurrence up through and including the visit; WC = waist circumference

As described in Hypotheses 5 and 6, race and menopausal status were added to all models, and planned covariates that were significantly correlated with depression or the outcomes at baseline were entered into significant models to examine their effect on the relationship of depression with WC and HOMA-IR.

Statistical Software. *Stata* was used for the GEE and Cox models; *SPSS* was used for all other analyses.

2.5 POWER ANALYSES

Power calculations are not readily available or reliable for the type of survival model conducted herein, and no power calculations are available for the GEE models. Thus, very conservative estimates of power were calculated for the basic analyses for this study. However, calculations do not generalize to the more sophisticated models (e.g., Cox proportional hazards, GEE) and are not necessarily valid indicators of the power for these analyses. For logistic regression analyses, power was computed using basic calculations for a logistic model based on a normal approximation. With an alpha-level of .05, the power to detect differences between women with and without a lifetime history or current diagnosis of major depression at baseline in the odds of having the metabolic syndrome from baseline through follow-up visit 05 was 0.50. These calculations were based on the univariate analyses which were limited to the 324 women for whom there were no missing data. The power to detect differences using the analyses which allow for missing

data (i.e., GEE and Cox models), was expected to be larger. In addition, the GEE model uses all available data from all participants and gains additional power by estimating both the “within-subject” and “between-subjects” effects and subsequently averaging them to create a single regression coefficient (Twisk, 2003). Power calculations were conducted using Power and Precision 2.0 (Biostat, 2000).

3. RESULTS

3.1 PRELIMINARY ANALYSES

Preliminary analyses showed that HOMA-IR values at each visit were highly positively skewed (see Table 2); values remained positively skewed (skewness = 2.11 - 3.55) after removing participants with diabetes. Thus, HOMA-IR values for the full sample were transformed by taking the log transformation of the original variable and transformed values were used in all further analyses.

Table 3 presents the inter-correlations among baseline covariates, depression (lifetime history / current at baseline), and the metabolic syndrome (baseline and cumulative through visit 05). Presence of the metabolic syndrome at baseline and cumulatively through visit 05 were positively associated with antidepressant use, age, WC, diabetes, and percent caloric intake from fat (baseline metabolic syndrome only); the metabolic syndrome (baseline and cumulative 05) was negatively associated with baseline levels of physical activity scores.

Baseline WC was positively associated with being Black (vs. White), perimenopausal status (vs. premenopausal), a diagnosis of alcohol use / dependence, age, total caloric intake and percent caloric intake from fat, and diabetes status. Greater WC was also associated with lower levels of physical activity and percent caloric intake from carbohydrates. Baseline HOMA values were positively associated with percent caloric intake from fat and diabetes, and values were negatively associated with physical activity and percent caloric intake from carbohydrates.

As seen in Table 3, major depression at baseline was positively associated ($p < .05$) with a diagnosis of any anxiety disorder, drug abuse / dependence, alcohol use / dependence, antidepressant use, and years of education. Table 4 presents the results of chi-square tests used to compare women with and without baseline depression (lifetime history / current) on frequency of other psychiatric diagnoses at baseline. Compared to women with no lifetime history or current diagnosis of major

depression at baseline, a greater percentage of women with baseline depression met criteria for a lifetime history or current diagnosis of drug abuse / dependence, alcohol abuse / dependence, and any anxiety disorder (all *p*'s < .05; see Table 4).

Table 3: Inter-correlations among baseline values and the cumulative index of the metabolic syndrome at visit 05 (ever from visit 00 – 05)

Variable	MD	Any D	Anx	Drug	ETOH	Meds	age	race	PA	kcal	% fat	% carb	smoke	MS 0	MS 5	HOMA	WC	DM	Edu	Men Stat
MD	...																			
Any D	.74[b]	...																		
Anxiety	.15[b]	.21[b]	...																	
Drug	.12[a]	.11[a]	.11[a]	...																
ETOH	.16[b]	.17[b]	.07	.46[b]	...															
Meds	.36[b]	.39[b]	.07	.06	.11[b]	...														
Age	-.01[c]	-.03[c]	-.12[a]	-.08	-.05	-.01	...													
Race	-.05[c]	-.08[c]	-.04	.11[a]	.02	-.15[b]	-.03	...												
PA	.01[c]	.02[c]	.00	.02	-.02	-.02	.00	-.21[b]	...											
Kcal	.01[c]	-.01[c]	-.01	.08	.07	.03	-.17[b]	.14[b]	.04	...										

Note: MD = major depression; Any D = major depression, minor depression, or dysthymia; Anx = any anxiety disorder; Drug = drug abuse / dependence; ETOH = alcohol use / dependence; Meds = antidepressants; PA = physical activity; MS = metabolic syndrome; WC = waist circumference; DM = diabetes; MenStat = menopausal status.
[a] = p< .05, [b] = p< .01, [c] = p >.10 (only listed for depression & MS); point-biserial for dichotomous x continuous; phi-correlation for dichotomous x dichotomous.

Table 3: (continued)

Variable	MD	Any D	Anx	Drug	ETOH	Meds	age	race	PA	kcal	% fat	% carb	smoke	MS 0	MS 5	HOMA	WC	DM	Edu	Men Stat
% fat	.05[c]	.04[c]	.03	.02	.03	-.06	.05	.12[a]	-.15[b]	.09	...									
% carb	-.03[c]	-.03[c]	.00	-.05	-.14[b]	.06	-.03	.01	.08	.06	-.84[b]	...								
Smoke	-.01[c]	-.02[c]	-.07	.11[a]	.22[b]	.04	-.06	.07	-.05	.07	.10[a]	-.12[a]	...							
MS 0	.07[c]	.06[c]	-.02[c]	.00[c]	.08[c]	.10[a]	.15[b]	.05[c]	-.16[b]	.06[c]	.11[a]	-.05[c]	-.03[c]	...						
MS 5	.10	.09c	-.02[c]	.06[c]	.11	.12[a]	.12[a]	.10	-.22[b]	.05[c]	.10	-.06[c]	.07[c]	.76[b]	...					
HOMA	-.05[c]	-.02[c]	-.05	.03	.00	.09	-.01	.05	-.19[b]	.01	.10[a]	-.11[a]	-.09	.39[b]	.33[b]	...				
WC	.04[c]	.02[c]	.06	.08	.16[b]	.07	.12[a]	.22[b]	-.25[b]	.10[a]	.15[b]	-.10[a]	-.05	.57[b]	.61[b]	.38[b]	...			
DM	.00[c]	.01[c]	-.03	.07	.00	.12[a]	.08	.09	-.17[b]	.00	.13[b]	-.11[a]	-.10[b]	.46[b]	.34[b]	.69[b]	.37[b]	...		
Edu	.11[a]	.10[a]	.08	-.04	-.05	.13[b]	-.09	-.07	-.01	-.03	-.10[a]	.09	-.17[b]	-.05[c]	-.09	.04	.00	.02	...	
Men Stat	-.04[c]	-.04[c]	-.00	-.11[a]	-.04	-.04	-.06	.0[c]	.02	.03	-.03	.02	-.08	.01[c]	.00	.04	-.10[a]	.02	.09	...

Note: MD = major depression; Any D = major depression, minor depression, or dysthymia; Anx = any anxiety disorder; Drug = drug abuse / dependence; ETOH = alcohol use / dependence; Meds = antidepressants; PA = physical activity; MS = metabolic syndrome; WC = waist circumference; DM = diabetes; MenStat = menopausal status.
[a] = p< .05, [b] = p< .01, [c] = p >.10 (only listed for depression & MS); point-biserial for dichotomous x continuous; phi-correlation for dichotomous x dichotomous.

Table 4: Chi-square tests showing differences in psychiatric diagnoses (lifetime history or current) by major depression diagnosis (lifetime history or current) at baseline evaluation.

Psychiatric Variable	n (%) within lifetime history / current major depression at visit 00	n (%) within no lifetime history / no current major depression at visit 00	Total N (%)
Lifetime history / current drug abuse / dependence at visit 00 (n = 421)	19 (12.6)*	16 (5.9)	35 (8.3%)
Lifetime history / current alcohol abuse / dependence at visit 00 (n = 420)	30 (20.0)**	24 (8.9)	54 (12.9%)
Lifetime history / current anxiety disorder at visit 00 (n = 421)	49 (32.6)**	52 (19.2)	101 (24%)

* Row Chi^2 comparing depression to no depression; $p < .05$; ** Row Chi^2 comparing depression to no depression; $p < .01$

Table 5 presents the results of chi-square tests used to compare women with and without baseline depression (lifetime history / current) and women with and without the metabolic syndrome (baseline and cumulative through 05) on frequency of baseline antidepressant use (lifetime history / current). Results showed that baseline antidepressant use was more common in women with the metabolic syndrome (baseline and cumulative at 05) as compared to women with no diagnosis of the metabolic syndrome, and in women with a lifetime history or current diagnosis of depression at baseline as compared to women with no depression (all *p*'s < .05).

Table 5: Lifetime history or current use of antidepressants at baseline by baseline depression and the cumulative index of the metabolic syndrome at visit 05 (ever from visit 00 - 05).

Lifetime history / current antidepressant use at visit 00	MS at visit 00 [1]		Cumulative MS from 00-05		Lifetime history or current MD at visit 00	
	Absent N (%)	Present N (%)	Absent N (%)	Present N (%)	Absent N (%)	Present N (%)
No	291 (86.6%)	66 (77.6%)	176 (87.6%)	97 (78.9%)	256 (94.5%)	101 (67.3%)
Yes	45 (13.4%)	19 (22.4%)*	25 (12.4%)	26 (21.1%)*	15 (5.5%)	49 (32.7%)**

Note: [1] MS = metabolic syndrome; MD = major depression;
* Row Chi^2 (comparing absent to present); $p < .05$; ** Row Chi^2 (comparing absent to present); $p < .01$

T-tests and chi-square tests were used to compare the demographic, psychiatric, and metabolic characteristics of participants with complete data for depression, the metabolic syndrome, and WC at all visits to women who were missing any of these variables at any visit. As seen in Table 6, women with missing data had a lower mean age and education level; they were more likely to be Black and less likely to be premenopausal at baseline. There were no differences in the prevalence of major depression or the metabolic syndrome at baseline; however, women with any missing data were more likely to have a current or past year diagnosis of major depression / subthreshold recurrence at follow-up visit 03 and more likely to have ever had the metabolic syndrome cumulatively from baseline through follow-up visit 05 (all *p*'s < .05; see Table 6).

3.2 MAIN ANALYSES – METABOLIC SYNDROME

For simplicity, findings for Hypothesis 5 (e.g., race, menopausal status, diabetes, antidepressants, and other psychiatric diagnoses) and Hypothesis 6 (e.g., health behaviors) are incorporated into the description of the results for Hypotheses 2-4 and 7-8.

Hypothesis 1: In comparison to subjects with no lifetime history or current diagnosis of major depression at baseline, subjects with major depression were expected to have greater frequency of the metabolic syndrome at baseline. As expected, the percentage of subjects with major depression at baseline who had the metabolic syndrome at baseline (24.0%) was slightly greater than the percentage of subjects without major depression who had the metabolic syndrome at baseline (18.1%). However, contrary to hypotheses, chi-square tests showed that this trend was not statistically significant ($\chi^2 = 2.10$, $p > .10$; see Table 7).

Table 6: Characteristics of participants missing data for depression, the metabolic syndrome, or waist circumference at any visit and participants with complete data for depression, the metabolic syndrome, and waist circumference at all visits.

	N (%) [1]	
	Not missing depression, MS, or WC at any visit	Missing depression, MS, or WC at any visit
Number of participants	227	194
Age (years)*	M = 45.86, SD = 2.49	M = 45.24, SD = 2.45
Self-Identified Ethnicity: Black / African-American**	63 (27.8%)	81 (41.8%)
Education (years)*	M = 15.22, SD = 2.17	M = 14.73, SD = 2.12
Premenopausal at Visit 00**	133 (59.1%)	84 (43.5%)
Major Depression or Subthreshold Recurrence		
Lifetime history / current at Visit 00	79 (34.8%)	71 (36.6%)
Visit 00 past year / current	21 (9.5%)	27 (14.0%)
Visit 01	34 (15.0%)	18 (11.5%)
Visit 02	35 (15.4%)	17 (10.7%)
Visit 03*	21 (9.3%)	26 (17.3%)
Visit 04	25 (11%)	19 (13.9%)
Visit 05	25 (11%)	23 (18.3%)
Metabolic Syndrome		
Visit 00	43 (18.9%)	42 (21.6%)
Visit 01	45 (19.8%)	37 (26.8%)
Visit 03	48 (21.1%)	24 (25.3%)
Visit 05	45 (19.8%)	15 (25.4%)
Ever from 00-05**	66 (29.1%)	57 (58.8%)
Incident through 05**	23 (12.5%)	15 (27.3%)
Waist Circumference (cm)		
Visit 00*	M = 86.45, SD = 15.00	M = 89.64, SD = 15.33
Visit 01	M = 87.50, SD = 15.46	M = 90.55, SD = 15.58
Visit 02*	M = 88.43, SD = 15.02	M = 92.20, SD = 15.88
Visit 03	M = 89.16, SD = 15.77	M = 91.56, SD = 15.62
Visit 04	M = 89.76, SD = 15.12	M = 91.48, SD = 14.99
Visit 05	M = 89.09, SD = 15.66	M = 92.19, SD = 15.33
HOMA-IR		
Visit 00	M = 2.76, SD = 4.39	M = 2.77, SD = 2.97
Visit 01	M = 3.04, SD = 5.53	M = 2.81, SD = 3.06
Visit 03	M = 3.10, SD = 5.76	M = 3.08. SD = 3.74
Visit 05	M = 2.93, SD = 4.41	M = 3.44, SD = 5.47

[1] M = mean; SD = standard deviation; MS = metabolic syndrome; WC = waist circumference

* T-tests (continuous) or Chi^2 (categorical) comparing missing to non-missing; groups differ significantly at $p<.05$.

** T-tests (continuous) or Chi^2 (categorical) comparing missing to non-missing; groups differ significantly at $p<.01$.

Table 7: Hypothesis 1: Baseline association between lifetime history or current major depression and the metabolic syndrome.

	Lifetime History or Current Major Depression at Visit 00			
Metabolic Syndrome at 00	Absent n (%)	Present n (%)	Chi^2 *	*p*-value
Absent	222 (82.2)	114 (75.5)		
Present	49 (18.1)	36 (24.0)		
Total	271	150	2.10	.15

* Chi^2 comparing depression to no depression.

Hypothesis 2a: In comparison to women with no depression at baseline, women with baseline depression (lifetime history / current) were expected to have greater odds of having the metabolic syndrome cumulatively from baseline – visit 05 (Figure 3a). As seen in Table 8, results of the univariate logistic regression model showed that women with major depression at baseline had 1.55 greater odds of having the metabolic syndrome at any point during the study than women with no baseline depression ($p < .10$). The association between depression and the metabolic syndrome became slightly stronger and significant after adjusting for baseline age and race (OR = 1.62; $p < .05$); age and Black race were also associated with greater odds of having the metabolic syndrome at any point during the study (*p's* < .10; see Table 8).

Separate multivariate models were constructed with each planned covariate that was significantly associated with baseline depression (lifetime history / current) or the metabolic syndrome (baseline or cumulative 05) in univariate analyses, as well as those covariates which differed significantly between women with and without baseline depression. Depression, age, and race were entered on step 1, followed by each of the covariates. As seen in Table 8, baseline depression continued to predict significantly greater odds of having the metabolic syndrome cumulatively over the course of the study, after controlling for baseline menopausal status, physical activity, percent calories from fat, and diabetes diagnosis, although the association between depression and the metabolic syndrome became stronger when physical activity was added to the model. There were no significant interactions between depression and any of these covariates (all *p*'s > .10; results not shown).

Table 8: Logistic regressions showing the association of baseline major depression (lifetime history / current) predicting cumulative index of the metabolic syndrome at visit 05 (ever from 00 – 05).

DV: Presence of MS ever from 00-05 [1]

	Variable	OR (95% CI)	*p*-value
Univariate (n = 324)			
Step 1:			
	Depression	1.55 (0.98, 2.46)	.064
Age and Race (n = 324)			
Step 1:			
	Depression	1.62 (1.01, 2.59)	.046
	Age	1.12 (1.02, 1.22)	.020
	Race (Black)	1.67 (1.02, 2.72)	.040
Menopausal Status			
Step 2:			
	Depression	1.63 (1.02, 2.62)	.042
	Age	1.12 (1.02, 1.22)	.021
	Race (Black)	1.66 (1.02, 2.71)	.043
	Menopausal status (early perimenopause)	1.12 (0.70, 1.79)	.629
Physical activity at visit 00 (n = 322)			
Step 2:			
	Depression	1.74 (1.07, 2.83)	.026
	Age	1.20 (1.02, 1.23)	.019
	Race	1.39 (0.84, 2.32)	.201
	Physical Activity	(-) 0.76 (0.65, 0.88)	<.0001
% kcal fat at visit 00 (n = 324)			
Step 2:			
	Depression	1.62 (1.01, 2.59)	.047
	Age	1.11 (1.02, 1.22)	.021
	Race	1.61 (0.99, 2.64)	.057
	% kcal fat	1.03 (0.99, 1.06)	.093

[1] DV = dependent variable; OR = odds ratio; CI = confidence interval

Table 8: (continued)

DV: Presence of MS ever from 00-05 [1]

	Variable	OR (95% CI)	*p*-value
History / current other psychiatric diagnosis at visit 00 (n = 323)			
Step 2:			
	Depression	1.53 (0.94, 2.48)	.087
	Age	1.12 (1.02, 1.23)	.020
	Race	1.59 (0.97, 2.61)	.066
	Alcohol use / abuse	1.75 (0.84, 3.65)	.135
	Drug use / abuse	1.03 (0.40, 2.69)	.949
	Any anxiety disorder	(-) 0.89 (0.50, 1.58)	.693
Antidepressant use at visit 00 (n = 324)			
Step 2:			
	Depression	1.37 (0.83, 2.28)	.219
	Age	1.12 (1.02, 1.23)	.018
	Race	1.79 (1.09, 2.94)	.022
	Antidepressants	1.86 (0.96, 3.59)	.067
Diabetes at visit 00 (n = 322) [2]			
Step 2:			
	Depression	1.75 (1.06, 2.88)	.029
	Age	1.11 (1.00, 1.22)	.042
	Race	1.55 (0.92, 2.62)	.102
	Diabetes	44.27 (5.84, 335.86)	<.0001

[1] DV = dependent variable; OR = odds ratio; CI = confidence interval

[2] Results were similar if participants with baseline diagnosis of diabetes (n=25) were eliminated rather than controlled for.

The association between depression and the metabolic syndrome was reduced and became marginal after controlling for baseline psychiatric diagnoses (anxiety disorder, alcohol abuse / dependence, drug abuse / dependence; OR = 1.53; $p < .10$); however, none of the psychiatric diagnoses was a significant factor in the model (all *p's* >.10; see Table 8). Results were similar when three separate models were constructed with each psychiatric diagnosis at baseline entered separately on step 2, although none of the psychiatric diagnosis was a significant predictor of the metabolic syndrome ($p > .10$ for each psychiatric diagnosis; results not shown), and depression remained a marginally significant or significant predictor of the metabolic syndrome in these models. As seen in Table 8, the association between depression and the metabolic syndrome was no longer significant when baseline antidepressant use was entered on step 2 ($p > .10$); antidepressant use was associated with approximately twice the odds of having the metabolic syndrome at some point over the course of the study ($p < .10$). There were no significant interactions between depression and any of these covariates (all *p's* > .10; results not shown).

Hypothesis 2b: In women who were free of the metabolic syndrome at baseline, women with baseline depression (lifetime history / current) were expected to have greater odds of developing the metabolic syndrome over the course of the follow-up period ("cumulative index" of incident cases, visit 01 – 05) as compared to women with no depression (Figure 3b). As seen in Table 9, results of the univariate logistic regression model showed that women with depression had 1.66 greater odds of developing the metabolic syndrome by the end of the study, as compared to women with no baseline depression; however, this effect was not significant ($p > .10$). Odds of developing the metabolic syndrome increased slightly after controlling for baseline age and race (OR = 1.74), although this effect was still not significant ($p > .10$; see Table 9). Menopausal status was not associated with the metabolic syndrome and did not affect the association between depression and the metabolic syndrome (results not shown).

Table 9: Logistic regressions showing the association of baseline major depression (lifetime history / current) predicting cumulative index of incident cases of the metabolic syndrome at visit 05 (ever from 01 – 05) in women who were free of the metabolic syndrome at baseline.

DV: Incident MS ever from 01 - 05 in participants free of MS at 00 [1, 2]

	Variable	OR (95% CI)	*p*-value
Univariate (n = 239)			
Step 1:			
	Depression	1.66 (.82, 3.35)	.160
Age and Race (n = 239)			
Step 1:			
	Depression	1.71 (.84, 3.48)	.137
	Age	1.08 (.94, 1.24)	.265
	Race	1.42 (.67, 3.00)	.357
Physical activity score at visit 00 (n = 238)			
Step 2:			
	Depression	1.77 (0.86, 3.63)	.196
	Age	1.09 (0.95, 1.25)	.244
	Race	1.09 (0.50, 2.40)	.828
	Physical activity	0.78 (0.62, 0.98)	.030

Note: [1] DV = dependent variable; OR = odds ratio; CI = confidence interval
[2] Results were similar if participants with baseline diagnosis of diabetes (n=25) were eliminated.

Hypothesis 3: In women who were free of the metabolic syndrome at baseline, participants with baseline depression (lifetime history / current) were expected to have greater risk for developing the metabolic syndrome across the five-year follow-up compared to women with no baseline depression (Figure 4). Among the 336 women who were free of the metabolic syndrome at baseline, a total of 38 women (11.3%) developed the metabolic syndrome over the course of the study; 22 first met criteria at follow-up visit 01, 13 first met criteria at visit 03, and 3 first met criteria at visit 05. The median follow-up length was 6 years with a range of 2 to 6 years. Chi-square and t-tests were used to compare characteristics of the 85 women who had the metabolic syndrome at baseline to the remaining 336 women who were used for the current analyses. Results showed that women with the metabolic syndrome at baseline were older and had lower physical activity scores (p's < .01), had greater percent caloric intake from fat (p < .05), and were more likely to report a lifetime history or current use of antidepressants at baseline (p < .05); there were no other significant group differences.

Within the 336 participants used for the current analyses, chi-square and t-tests were used to compare characteristics of women who developed the metabolic syndrome to those who remained free of the metabolic syndrome. Results showed that women who developed the metabolic syndrome had lower physical activity scores (p < .05) and were slightly more likely to be smokers (p = .09) at baseline; there were no other significant group differences.

Results of the univariate and multivariate Cox models conducted to examine the association between baseline depression and risk for developing the metabolic syndrome are displayed in Table 10. Univariate results showed that women with depression were 60% more likely to develop the metabolic syndrome over the course of the follow-up visits than women with no baseline depression; however, although this trend was in the predicted direction, it was not statistically significant (p = 0.15). Event-free Kaplan-Meier survival curves for women with and without a baseline diagnosis of depression are presented in Figure 9. As demonstrated in Figure 9, survival curves for women with and without depression were proportional, and women with a baseline diagnosis of depression had a lower "event-free survival rate" than women with no depression, indicating that women with baseline depression were less likely to remain free of the metabolic syndrome over the course of the study.

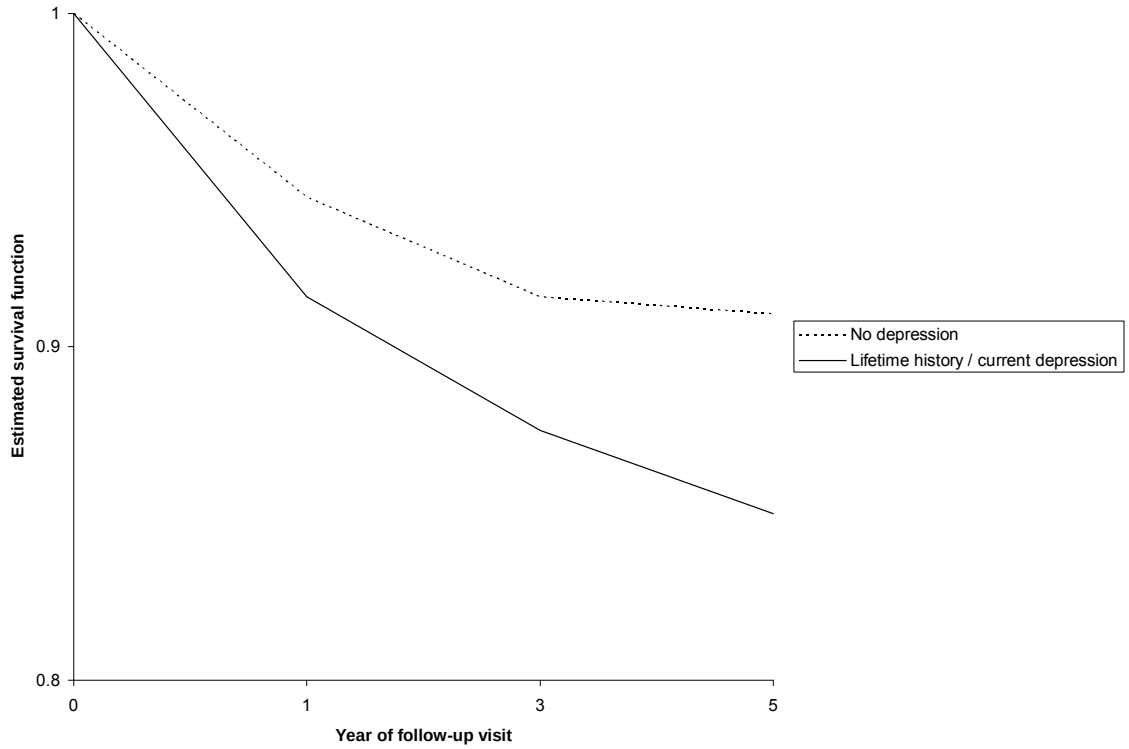

Figure 9: Event-free Kaplan-Meier survival curves for women with and without a lifetime history / current diagnosis of depression at baseline

As seen in Table 10, results were similar after adding baseline age and race to the model, such that a lifetime history or current diagnosis of depression at baseline was associated with 66% greater risk of developing the metabolic syndrome over the course of the follow-up (p = .12), although this difference was not significant; older age at baseline was associated with marginally greater risk of developing the metabolic syndrome across follow-up (p < .10). This model (depression, age, and race) was used as the "basic" model for all further analyses. Baseline menopausal status (early perimenopause compared to premenopause) was not associated with risk for the metabolic syndrome (p > .10). In the fully adjusted model controlling for age, race, antidepressant use, physical activity, percent caloric intake from fat, and psychiatric diagnoses, the risk associated with major depression decreased to 56% (p = .22); physical activity was the only significant covariate in this model (p < .05; see Table 10). To make the relationship between physical activity and the metabolic syndrome more meaningful, a standardized score (z-score; mean of 0) was created for physical activity and the model was rerun with this standardized score.

Results of this model showed that the risk for developing the metabolic syndrome decreased by approximately 30% with every one standard deviation increase in the physical activity score (see Table 10). To create the most parsimonious model, covariates which were not related to the metabolic syndrome at the $p < .10$ level in the fully adjusted model were removed. In this final model, baseline physical activity remained a significant predictor of risk for the metabolic syndrome, and the risk associated with major depression was very similar to that in the "basic" model ($p > .10$; see Table 10).

Hypothesis 4: A lifetime history or current diagnosis of depression (major depression or subthreshold recurrence) at each visit (visits 00, 01, 03, and 05) was expected to be associated with greater odds of having the metabolic syndrome at each visit (visits 00, 01, 03, and 05; Figure 5a). Results of univariate and multivariate GEE models are presented in Table 11. Contrary to our hypothesis, depression was not associated with greater odds of having the metabolic syndrome in univariate or multivariate models (p's > .50). Age was a marginally significant predictor of the metabolic syndrome, such that older age was associated with slightly greater odds of having the metabolic syndrome ($p < .10$); there was no significant interaction between age and depression ($p > .10$; results not shown). Similar results were found when antidepressant use (baseline – visit 05) or menopausal status (visits 01-05), were added to the model (see Table 11). In addition to age and race, diabetes status at each visit was also added to the multivariate model. Although diabetes was associated with significantly greater odds of having the metabolic syndrome (OR = 8.02; 95% CI = 4.46, 14.42; $p < .001$), depression, age, and race were not significant factors in this model, and there was no interaction between depression and age (results not shown). Similarly, results of analyses conducted with women who were free of diabetes at baseline did not differ from those reported with the full sample (results not shown).

Table 10: Cox proportional hazard model of the association between baseline major depression (lifetime history or current) and risk of developing the metabolic syndrome through visit 05.

Model (n = 336)	Predictor Variable	Hazard Ratio (95% CI) [1,2]	*p*-value
1	Lifetime history / current MD at visit 00	1.60 (0.85, 3.04)	.150
2	Lifetime history / current MD at visit 00	1.65 (0.87, 3.13)	.130
	Age at visit 00	1.11 (0.99, 1.26)	.080
3	Lifetime history / current MD at visit 00	1.66 (0.87, 3.15)	.120
	Age at visit 00	1.12 (0.99, 1.26)	.078
	Race (Black)	1.10 (0.56, 2.15)	.784
4	Lifetime history / current MD at visit 00	1.67 (0.88, 3.12)	.120
	Age at visit 00	1.11 (0.99, 1.26)	.080
	Race (Black)	1.09 (0.56, 2.14)	.802
	Menopausal status at visit 00 (early perimenopause)	0.81 (0.43, 1.54)	.533
5	Lifetime history / current MD at visit 00	1.56 (0.77, 3.20)	.022
	Age at visit 00	1.13 (0.99, 1.28)	.065
	Race (Black)	0.87 (0.42, 1.80)	.699
	Lifetime history / current antidepressant use at visit 00	1.31 (0.52, 3.28)	.567
	Physical activity score at visit 00	0.80 (0.65, 0.99)	.036
		z-score = 0.69	
	Percent fat intake at visit 00	0.99 (0.95, 1.03)	.679
	Lifetime history / current anxiety disorder at visit 00	0.63 (0.27, 1.48)	.286
	Lifetime history / current alcohol at visit 00	1.50 (0.58, 3.87)	.399
	Lifetime history / current drug at visit 00	1.57 (0.53, 4.71)	.418
6	Lifetime history / current MD at visit 00	1.64 (0.87, 3.12)	.129
	Age at visit 00	1.13 (0.99, 1.27)	.062
	Race (Black)	0.88 (0.44, 1.77)	.713
	Physical activity score at visit 00	0.80 (0.65, 0.99)	.036

Note: [1] CI = confidence interval; MD = major depression
[2] Results were similar when sample was restricted to participants with no diabetes at baseline (n = 334).

Table 11: Results of Generalized Estimating Equation (GEE) models showing the relationship between depression (at visits 00, 01, 03, and 05) and odds of having the metabolic syndrome (at visits 00, 01, 03, and 05) [1]

Model (n = 421)	Predictor Variable	Relative odds of having the MS (95% CI) [2]	*p*-value
1	MDE or subthreshold recurrence	1.03 (0.82, 1.30)	.790
2	MDE or subthreshold recurrence	1.09 (0.85, 1.38)	.500
	Age	1.03 (0.99, 1.07)	.062
3	MDE or subthreshold recurrence	1.09 (0.85, 1.39)	.497
	Age	1.04 (0.99, 1.07)	.056
	Race (Black)	1.34 (.87, 2.07)	.188
4	MDE or subthreshold recurrence	1.08 (0.85, 1.38)	.537
	Age	1.05 (1.01, 1.10)	.029
	Race (Black)	1.36 (0.88, 2.09)	.171
	Menopausal status (compared to pre / early peri)		
	Late peri	0.71 (0.47, 1.06)	.094
	Post / Surgical	0.92 (0.67, 1.27)	.613
	Unknown due to HRT	0.84 (0.59, 1.19)	.323
5	MDE or subthreshold recurrence	1.11 (0.86, 1.44)	.414
	Age	1.03 (0.99, 1.07)	.063
	Race (Black)	1.36 (0.88, 2.10)	.165
	Antidepressant use	1.01 (0.71, 1.44)	.945

Note: [1] Depression, metabolic syndrome, age, menopausal status, and antidepressant use all treated as time-varying variables; [2] MS = metabolic syndrome; CI = confidence interval; MDE = major depressive episode; HRT = hormone replacement therapy

Time-lag

A lifetime history or current diagnosis of depression at any point up to and including each visit (cumulative depression, lifetime and visits 00, 02, and 04) was expected to be associated with greater odds of having the metabolic syndrome at the following visit (visits 00, 01, 03, and 05), independent of concurrent age and race (Figure 5b). Contrary to our hypothesis, the cumulative index of depression was not associated with significantly greater odds of having the metabolic syndrome at the following visit in univariate or multivariate models (*p*'s > .10; see Table 12).

Table 12: Results of Generalized Estimating Equation (GEE) time-lag models showing the relationship between a cumulative index of depression (presence of depression up through and including the current visit; lifetime, 00, 02, and 04) and odds of having the metabolic syndrome at the following visit (visits 00, 01, 03, and 05) [1]

Model (n = 421)	Predictor Variable	Relative odds of having the MS at the next visit (95% CI) [2]	*p*-value
1	Cumulative depression up through and including each visit	1.15 (0.86, 1.55)	.341
2	Cumulative depression up through and including each visit	1.10 (0.81, 1.50)	.532
	Age	1.02 (0.99, 1.06)	.193
3	Cumulative depression up through and including each visit	1.11 (0.81, 1.51)	.508
	Age	1.02 (0.99, 1.06)	.180
	Race (Black)	1.35 (0.88, 2.09)	.170
4	Cumulative depression up through and including each visit	1.12 (0.82, 1.52)	.485
	Age	1.04 (0.99, 1.09)	.068
	Race (Black)	1.37 (0.89, 2.11)	.155
	Menopausal status (compared to pre / early peri)		
	Late Peri	0.71 (0.47, 1.07)	.098
	Post / Surgical	0.90 (0.65, 1.27)	.525
	Unknown due to HRT	0.80 (0.56, 1.14)	.223
5	Cumulative depression up through and including each visit	1.11 (0.81, 1.52)	.513
	Age	1.02 (0.99, 1.06)	.214
	Race (Black)	1.39 (0.90, 2.15)	.138
	Antidepressant use	1.06 (0.75, 1.50)	.733

Note: No significant interactions with race or age.
[1] Cumulative depression, metabolic syndrome, age, menopausal status, and antidepressant use all treated as time-varying variables; [2] MS = metabolic syndrome; CI = confidence interval; HRT = hormone replacement therapy

3.2.1 Additional Analyses on the Metabolic Syndrome

While results of analyses with depression and the metabolic syndrome were in a direction that is consistent with our hypotheses, there was often only a trend for statistical significance. Based on preliminary findings that women who had taken antidepressants at any point up to and including the baseline visit were more likely to have the metabolic syndrome at baseline and cumulatively through follow-up visit 05 (compared to women who had never taken antidepressants), we explored the effect of adding women who had taken antidepressants but did not meet criteria for a major depressive episode (n =15 at baseline) to the "depression" group. The term "depression" in this section will be used to refer to women with a lifetime history or current diagnosis of major depression, subthreshold recurrence, or antidepressant use.

As seen in Table 1 of Appendix B, with the addition of women who had taken antidepressants at baseline, the proportion of women with depression at baseline who met baseline criteria for the metabolic syndrome (24.2%) was marginally greater than the proportion of women who were free of depression and met criteria for the metabolic syndrome (17.7%; $p < .10$). Similarly, results of the univariate logistic regression model showed that baseline depression was associated with 1.65 times greater odds of having the metabolic syndrome at some point over the course of the study ($p < .05$); this effect became stronger after controlling for baseline age and race (see Appendix B, Table 2). In addition, in women who were free of the metabolic syndrome at baseline, the univariate logistic regression model showed that baseline depression was associated with 1.79 greater odds of developing the metabolic syndrome ($p = .10$); the odds ratio increased and became marginal after controlling for baseline age and race ($p < .10$; see Appendix B, Table 2).

Cox survival models, paralleling those outlined in Hypothesis 3, were constructed to explore the effect of the newly defined depression variable on risk of developing the metabolic syndrome over the course of the follow-up visits. Consistent with the findings reported under Hypothesis 3, univariate and multivariate Cox models showed that depression was associated with increased odds of developing the metabolic syndrome over the course of the study. Notably, as seen in Table 3 of Appendix B, the effect of depression was now stronger and marginally significant, such that women with baseline depression

were 73% more likely to develop the metabolic syndrome over the course of the follow-up period than women with no depression at baseline (p = 0.09 for univariate model; results of multivariate models controlling for age and race, menopausal status, and physical activity were similar).

Results of GEE models conducted with the newly defined depression variable (coded as a time-varying IV which included depression or antidepressant use at each visit) were no different from those with depression alone, such that depression / antidepressant across time use was not associated with odds of the metabolic syndrome across time in univariate (OR = 1.05; 95% CI = 0.83, 1.31; p > .50) or multivariate (OR = 1.09; 95% CI = 0.86, 1.38; p > .50, controlling for age at each visit and race) models (results not shown).

3.3 SECONDARY ANALYSES - CENTRAL ADIPOSITY AND INSULIN RESISTANCE

Hypothesis 7: Baseline depression (lifetime history / current) was expected to be associated with greater central adiposity and insulin resistance at baseline and follow-up visit 05 (Figures 6 and 7). Results of univariate and multivariate GLMs testing for differences in mean WC (baseline and visit 05) between women with and without baseline depression are presented in Table 13. Contrary to our hypothesis, there were no significant differences between depressed and non-depressed women in mean WC at baseline in univariate or multivariate models (p's > .10). Greater age and Black race were significant predictors of greater baseline WC (p's < .05; see Table 13). Although women with a baseline diagnosis of depression (lifetime history or current) had slightly greater mean WC at visit 05 than women with no depression at baseline, this difference was not statistically significant (p = .12; see Table 13). However, the difference between depressed and non-depressed women in mean WC at visit 05 became stronger and marginally significant after controlling for baseline age and race (p = .053). Black race was also associated with significantly greater WC at visit 05 (p < .001). Interestingly, the association between depression and WC at visit 05 was no longer significant when antidepressant use was entered into the model; there was no significant interaction between antidepressant use and depression.

We explored whether the effect of depression on mean WC at baseline and visit 05 differed between Blacks and Whites by incorporating a race-by-depression interaction term into the above

models. The interaction was not significant in the model of baseline WC; however, the interaction showed a nonsignificant trend in the model of WC at visit 05 (p=.113), suggesting that the relationship between depression and WC may differ between Blacks and Whites. Simple-effects analyses conducted with Blacks and Whites separately showed that, within Blacks, women with depression had significantly greater WC at follow-up visit 05 than women who were free of depression at baseline ($p < .05$). However, depression was not a significant predictor of WC in Whites (see Table 13).

Table 14 presents results of univariate and multivariate (controlling for baseline age and race) GLMs testing for differences in HOMA values (log-transformed; baseline and visit 05) between women with and without baseline depression. Contrary to our hypothesis, there were no significant differences between depressed and non-depressed women in HOMA values at baseline or visit 05 (p's > .50; univariate and multivariate models). Findings did not change when participants who met criteria for diabetes at baseline or visit 05 were removed from the sample (results not shown). Results showed that Blacks had significantly greater mean HOMA-IR values at baseline and visit 05, compared to Whites (p's < .05); older age at baseline predicted significantly greater HOMA-IR values at visit 05 ($p < .01$). We explored whether the effect of depression on HOMA-IR values differed between Blacks and Whites by incorporating a race-by-depression interaction term into the baseline and visit 05 models; these interactions were not significant (p's > .10; results not shown).

Table 13: Results of General Linear Model ANOVAs showing differences in mean waist circumference at baseline and visit 05 in women with and without baseline depression (lifetime history / current)

	Mean (*SD*) [1]			
WC Assessment			*F*	*p*-value
WC at visit 00 [2]				
	No lifetime history / no current major depression at visit 00	Lifetime history / current major depression at visit 00		
N	266	149		
Depression	87.48 (14.51)	88.64 (16.43)	0.56	.456
Depression			0.99	.321
Age at visit 00			6.40	.012
Race (Black)			21.31	<.0001
Depression			1.33	.250
Age at visit 00			6.53	.011
Race (Black)			20.95	<.0001
Depression*Race			0.40	.529
WC at visit 05 (N=269) [2]				
	No lifetime history / no current major depression at visit 00	Lifetime history / current major depression at visit 00		
N	199	114		
Depression	88.89 (14.85)	91.78 (16.76)	2.50	.115
Depression			3.78	.053
Age at visit 00			2.77	.097
Race (Black)			20.19	<.0001
Depression			0.94	.333
Age at visit 00			2.97	.086
Race (Black)			22.60	<.0001
Antidepressant use [2]			4.42	.036
Depression			5.73	.017
Age at visit 00			3.10	.079
Race (Black)			22.81	<.0001
Depression*Race			2.53	0.113
Blacks (n)	71	34		
Depression	92.73 (13.93)	99.94 (18.23)	4.97	.028
Age at visit 00			0.02	.884
Whites (n)	128	80		
Depression	86.76 (14.97)	88.32 (14.91)	0.57	.471
Age at visit 00			3.95	.048

Note: [1] SD = standard deviation; WC = waist circumference; [2] Lifetime history / current at visit 00, no significant interaction between antidepressants and race.

Table 14: Results of General Linear Model ANOVAs showing differences in mean HOMA-IR levels at baseline and visit 05 in women with and without baseline depression (lifetime history or current)

	Raw Mean (*SD*) [1]			
HOMA-IR Assessment			*F*	*p*-value
HOMA-IR at 00 (N=412) [2]				
	No lifetime history / no current major depression at visit 00	Lifetime history / current major depression at visit 00		
N	264	148		
Depression	2.91 (4.46)	2.50 (2.14)	0.28	.600
Depression			0.13	.715
Age at visit 00			0.88	.350
Race (Black)			9.18	.003
HOMA-IR at 05 (N=269) [2]				
	No lifetime history / no current major depression at visit 00	Lifetime history / current major depression at visit 00		
N	176	93		
Depression	3.02 (4.87)	3.08 (4.26)	0.28	.598
Depression			0.35	.553
Age at visit 00			7.45	.007
Race (Black)			5.52	.020

Note: [1]SD = Standard Deviation

[2] Analyses conducted with log-transformed HOMA values; means and standard deviations presented for raw scores. Values were transformed with sample that included participants with diabetes; results were similar if participants with diabetes were removed from analyses.

Hypothesis 8: A diagnosis of major depression or subthreshold recurrence (at each visit) was expected to be associated with higher WC (at each visit) across time (Figure 8a). As shown in Table 15, results of GEE models showed that depression was associated with significantly lower WC in the univariate ($p < .001$) and multivariate model ($p < .05$; controlling for age at each visit and race). Age and Black race were significant predictors of greater WC (p's < .001); menopausal status was not a significant predictor when added to the model with age and race ($p > .10$).

All planned covariates which were significantly correlated with major depression or WC at baseline were entered into the multivariate models to examine their effect on the relationship between depression and WC. As seen in Table 15, the inverse association between depression and WC remained significant in this fully adjusted model ($p < .05$), along with age (time-varying), Black race, antidepressant use (time-varying), and baseline physical activity (p's < .05). There was no significant depression-by-age interaction ($p > .10$; results not shown). We explored whether the association between depression and WC varied by race or antidepressant use; neither interaction term was significant (p's > .10, results not shown). To create the most parsimonious model, analyses were conducted including only those covariates which were significant at the $p < .10$ level in the full model; results did not differ from the results of the full model (results not shown). Four separate models were also constructed for each of the four significant covariates (activity (baseline), total calories (baseline), antidepressant use (time varying), and any anxiety disorder (time-varying)) added to the model with age, race, and depression. The inverse association between depression and WC continued to be significant in each of these models (p's < .05; results not shown).

Post-hoc analyses were used to explore potential explanations for the inverse association between depression and WC. Although there was no significant interaction between depression and race, follow-up analyses were conducted with the sample stratified by race to explore whether the association between depression and WC across time varied between Blacks and Whites. Results showed that the negative association was marginally significant in Whites, but not Blacks, suggesting that this inverse relationship may be particularly true for Whites (results not shown). Results of analyses conducted with the sample stratified by baseline BMI suggested that the inverse association between depression and WC may be particularly salient in women with a "low" (BMI < 30) rather than "high" (> 30)

Table 15: Results of Generalized Estimating Equation (GEE) models showing the relationships between depression at each visit and waist circumference at each visit [1]

Model (n = 421)	Predictor Variable	Regression coefficient (95% CI) [2]	*p*-value
	MDE or subthreshold recurrence	-1.50 (-2.2, -0.84)	<.001
1	MDE or subthreshold recurrence	-0.84 (-1.50, -0.18)	.013
	Age	0.51 (0.40, 0.62)	<.001
3	MDE or subthreshold recurrence	-0.84 (-1.51, -0.17)	.014
	Age	0.51 (0.40, 0.62)	<.001
	Race (Black)	6.51 (3.57, 9.44)	<.001
4	MDE or subthreshold recurrence	-0.85 (-1.52, -0.18)	.013
	Age	0.51 (0.38, 0.64)	<.001
	Race (Black)	6.53 (3.59, 9.47)	<.001
	Menopausal status (compared to pre / early peri)		
	Late peri	0.42 (-0.49, 1.34)	.367
	Post / Surgical	-0.28 (-1.16, 0.58)	.524
	Unknown due to HRT	0.60 (-.022, 1.42)	.150
5	MDE or subthreshold recurrence	-0.92 (-1.63, -0.21)	.01
	Age	0.50 (0.39, 0.61)	<.001
	Race (Black)	6.43 (3.48, 9.37)	<.001
	Antidepressant use	1.04 (0.02, 2.07)	.046
6	MDE or subthreshold recurrence	-0.85 (-1.57, -0.12)	.022
	Age	0.48 (0.37, 0.60)	<.001
	Race (Black)	4.69 (1.66, 7.72)	.002
	Antidepressant use	1.06 (0.03, 2.09)	.043
	Smoker	-0.23 (-0.77, 0.31)	.407
	Physical activity level at visit 00	-1.64 (-2.48, -0.81)	<.001
	Total kcal at visit 00	0.002 (-0.00, 0.004)	.056
	Percent fat intake at visit 00	0.09 (-0.28, 0.46)	.626
	Percent carbohydrate intake at visit 00	-0.07 (-0.40, 0.25)	.654
	Any anxiety disorder	-0.78 (1.59, 0.03)	.058
	Alcohol abuse or dependence	1.36 (-2.07, 0.89)	.435
	Drug abuse or dependence	-0.02 (-1.99, 2.03)	.981

Note: [1] Depression, metabolic syndrome, age, menopausal status, antidepressant use, smoking status, and psychiatric disorders all treated as time-varying variables
[2] CI = confidence interval; MDE = major depressive episode; HRT = hormone replacement therapy

BMI at baseline (results not shown). Statistical and graphical examination of the data showed that the inverse association of depression with WC was not due to outliers, violations of normality, heteroscedasticity, nonlinearity, or missing data.[2]

Time-lag

A lifetime history or current diagnosis of depression at any point up to and including each visit (cumulative depression; lifetime and visits 00-04) was expected to be associated with increased waist circumference at the following visit (visits 00-05), independent of concurrent age and race (Figure 8b). As seen in Table 16, a diagnosis of depression at any point up through and including each visit was associated with increased WC at the following visit in univariate analyses ($p < .05$), although this effect was no longer significant after controlling for age (concurrent with WC) and race ($p > .10$). Age and Black race were significantly associated with greater WC across time (p's < .001; see Table 16). There was no effect of menopausal status ($p > .10$), and there was no significant interaction between depression and age or race (p's > .10; results not shown).

Table 16: Results of Generalized Estimating Equation (GEE) time-lag models showing the relationship between a cumulative index of depression at each visit (presence of depression up through and including the current visit; lifetime – visit 04) and waist circumference at the following visit (visits 00 – 05) [1]

Model (n = 421)	Predictor Variable	Regression coefficient (95% CI) [2]	*p*-value
1	Cumulative depression up through and including each visit	1.56 (0.50, 2.61)	.004
2	Cumulative depression up through and including each visit	0.15 (-0.91, 1.21)	.786
	Age	0.52 (0.41, 0.63)	<.001
4	Cumulative depression up through and including each visit	0.18 (-0.90, 1.25)	.749
	Age	0.53 (0.41, 0.64)	<.001
	Race (Black)	6.51 (3.57, 9.46)	<.001
5	Cumulative depression up through and including each visit	0.14 (-0.93, 1.21)	.799
	Age	0.53 (0.39, 0.66)	<.001
	Race (Black)	6.53 (3.58, 9.48)	<.001
	Menopausal status (compared to pre / early peri)		
	Late peri	0.49 (-0.43, 1.41)	.300
	Post / Surgical	-0.27 (-1.15, 0.62)	.560
	Unknown due to HRT	0.58 (-0.25, 1.41)	.174

Note: No significant interactions with race or age.
[1] Cumulative depression, waist circumference, age, and menopausal status all treated as time-varying variables
[2] CI = confidence interval; HRT = hormone replacement therapy

4. DISCUSSION

The purpose of the current study was to investigate the relationship between clinical depression and the metabolic syndrome and its core components of central adiposity and insulin resistance in a community-based sample of middle-aged women over a 6-year period. This question was addressed in several ways. First, we examined whether depression was associated with the metabolic syndrome, central adiposity, and insulin resistance at baseline (Figures 2 and 6) and across time (Figures 5a and 8a). Second, to help delineate the temporal sequence of the relationship between depression and the metabolic syndrome, we examined whether depression predicted increased risk of having or developing the metabolic syndrome in subsequent years of evaluation or over the course of the study (Figures 3a/b, 4, and 5b) and whether depression similarly predicted elevated central adiposity and insulin resistance in subsequent years of evaluation (Figures 7 and 8b). Finally, we explored whether these associations were independent of race, menopausal status, and potential confounding variables (e.g., diabetes, other psychiatric diagnoses, antidepressants), and we examined whether health behaviors accounted for the relationship between depression and the metabolic syndrome.

4.1 SUMMARY OF FINDINGS

Is depression concurrently associated with the metabolic syndrome, central adiposity, and insulin resistance at baseline and across time?

Contrary to hypotheses, while the metabolic syndrome at baseline was more common among women with a lifetime history or current diagnosis of depression at baseline (Figure 2), this difference was not statistically significant. Similarly, there was no significant association between depression at each

visit and the metabolic syndrome at that same visit, across the course of the study (Figure 5a). Regarding the hypothesized association of baseline depression with WC and insulin resistance, results showed that depression was not associated with WC or insulin resistance at baseline. Although we hypothesized that depression would be associated with greater WC across time (Figure 8a), results of longitudinal analyses showed that depression was inversely related to concurrent measures of waist circumference across time, and that this association was particularly salient in women with a BMI < 30 kg/m^2 and in Whites.

Does depression predict greater risk of having or developing the metabolic syndrome, increased central adiposity, and insulin resistance over the course of time and during subsequent years?

As hypothesized, baseline depression predicted greater odds of having the metabolic syndrome over the course of the study (visit 00 – 05; Figure 3a). However, in contrast to our hypotheses, depression at any point up through and including each year of observation ("cumulative" depression) was not associated with greater odds of having the metabolic syndrome during the following year of observation (Figure 5b). In women who were free of the metabolic syndrome at baseline, we hypothesized that a lifetime history or current diagnosis of depression at baseline would predict increased risk of developing the metabolic syndrome over the course of the study (Figures 3b and 4). Although results overall showed that depression at baseline was associated with approximately 60% greater risk of developing the metabolic syndrome, the effects were not statistically significant.

Consistent with our hypothesis, baseline depression was associated with greater waist circumference at visit 05 (Figure 7), but this was marginally significant only after controlling for baseline age and race. As predicted, the cumulative index of depression at each year of observation was associated with greater waist circumference at the following year of observation (Figure 8b); however this association was reduced to a nonsignificant trend upon controlling for age and race. Contrary to hypotheses, baseline depression was not associated with insulin resistance at follow-up visit 05.

Are the associations independent of race, menopausal status, diabetes, other psychiatric diagnoses, and use of antidepressants?

Descriptive Variables

As hypothesized, there were no race differences in the association between depression and the metabolic syndrome. Although the interaction between race and depression was not significant in any model, results of exploratory analyses suggested that the positive association between baseline depression and waist circumference at the final visit (Figure 7) may be stronger in Blacks, whereas the inverse association between depression and concurrent measures of WC across time (Figure 8a) may be stronger in Whites. Consistent with our expectations, the relationships of depression with the metabolic syndrome and central adiposity were independent of menopausal status and diabetes. No hypotheses were made regarding the effects of age. Nevertheless, in general, results showed that the associations of depression with the metabolic syndrome or waist circumference were strengthened upon controlling for age; however, age accounted for the positive association between the cumulative index of depression at each visit and waist circumference at the following visit.

Psychiatric Diagnoses and Antidepressant Use

The association between baseline depression and the metabolic syndrome at visit 05 was reduced when other baseline psychiatric diagnoses (e.g., anxiety disorders, alcohol abuse / dependence, drug abuse / dependence) were entered simultaneously into the model. However, none of the other psychiatric disorders was a significant predictor of the metabolic syndrome in the full model or when entered alone into separate models with depression, age, and race.

Lifetime history or current use of antidepressants at baseline was positively associated with the metabolic syndrome at baseline and cumulatively through visit 05, as well as elevated waist circumference at baseline and follow-up visit 05. However, baseline antidepressants did not predict risk of developing the metabolic syndrome, and antidepressant use across time was not associated with the metabolic syndrome across time. Interestingly, the associations of baseline depression with the cumulative index of the metabolic syndrome at visit 05 (Figure 3a) and waist circumference at visit 05 (Figure 7), were no longer significant when baseline antidepressant use was entered into the model. One possible interpretation of these findings is that antidepressants may account for the effect of baseline

depression on the metabolic syndrome over time. Nevertheless, if antidepressants were a mechanism by which depression influenced the metabolic syndrome, one would expect that antidepressants would predict increased risk of developing the metabolic syndrome. Given that over 75% of the women who reported antidepressant use at baseline also met criteria for depression at baseline, it is plausible that antidepressant use may simply be a marker of depression, rather than a mechanism. Consistent with this hypothesis, post-hoc analyses showed that the effect of baseline depression on the odds of having and developing the metabolic syndrome over time was strengthened when women who had taken antidepressants but did not meet diagnostic criteria for depression were added to the "depression" group.

Although antidepressants were associated with greater waist circumference, they did not influence the inverse association between concurrent associations of depression and waist circumference across time (Figure 8a), and the addition of women who had taken antidepressants at baseline to the baseline depression group did not affect this association (results not shown).

Do health behaviors reduce the association of depression with the metabolic syndrome, central adiposity, and insulin resistance?

Although physical activity was not associated with baseline depression, the effect of baseline depression on odds of developing the metabolic syndrome increased when baseline physical activity was entered into the model. Post-hoc analyses, conducted with the sample stratified by "high" and "low" (median split) levels of physical activity, suggested that the effect of depression on odds of having or developing the metabolic syndrome over time was particularly salient in women with low levels of physical activity (results not shown). Physical activity did not reduce or account for the associations between depression and waist circumference.

Although there was an indication that caloric intake and percentage of calories from fat may have a small, adverse effect on the metabolic syndrome and central adiposity, the results overall suggest that dietary intake does not influence the association of depression with the metabolic syndrome or central adiposity. While smoking tended to be associated with a lower waist circumference at baseline, it did not predict greater waist circumference and did not account for the associations between depression and waist circumference.

4.1.1 Summary of Depression, the Metabolic Syndrome, and Central Adiposity

Overall, this study provides some preliminary evidence that clinical depression may be related to the metabolic syndrome and central adiposity in a community sample of Black and White middle-aged women undergoing the menopausal transition. However, when considering these findings and comparing them with the current literature, it is important to note that the conclusions about the nature of these associations vary according to the type of analytic strategy and the outcome of interest.

Results of the longitudinal analyses which examined whether baseline depression predicted the odds of having the metabolic syndrome over the course of the study (Figure 3a), and whether baseline depression increased risk of developing the metabolic syndrome during follow-up (Figures 3b and 4), showed a trend indicating that clinical depression may adversely influence risk of the metabolic syndrome over time. In contrast, the longitudinal analyses which examined the concurrent associations between a cumulative index of depression and the metabolic syndrome at the subsequent visit across time were not significant (Figure 5b), and the cross-sectional baseline analyses (Figure 2) and longitudinal analyses of the associations between repeated measurements of depression and the metabolic syndrome across time (Figure 5a) showed no significant effects. One potential interpretation of these findings is that clinical depression may have a "long-term" adverse effect on risk of having or developing the metabolic syndrome at a later point in time, but depression and the metabolic syndrome may not be related in the "short-term" and they may not "track" together over time.

Findings of the relationship between depression and central adiposity were similarly dependent upon the nature of the question and the statistical model. Results of the analyses which examined whether baseline depression predicted increased waist circumference 5 years later (Figure 7) provide limited evidence that clinical depression may adversely influence waist circumference at a later point in time. In addition, the longitudinal analyses of the relationship between the "cumulative index" of depression at each visit and waist circumference at the subsequent visit (Figure 8b) showed a nonsignificant trend in the hypothesized direction. Together, these results suggest that depression may adversely affect the development of central adiposity, but this adverse effect may become more prominent with time.

Cross-sectional analyses showed no relationship between depression and waist circumference at baseline (Figure 6); however, longitudinal models of the associations between repeated measurements of depression and waist circumference across time (Figure 8a) suggest that depression may be inversely associated with central adiposity across time. This finding can be interpreted in two ways: first, depression may be related to lower concurrent measures of central adiposity across time; second, changes in depression (e.g., from not depressed to depressed) within women may be associated with decreases in central adiposity within that same woman. Given that depressive episodes can be accompanied by changes in appetite and subsequent decreases in weight, it is possible that these results reflect this more "acute" effect of depression on weight, as opposed to the longer-term adverse effect of depression on the development of central adiposity.

4.2 INTEGRATION WITH CURRENT LITERATURE

As aforementioned, this is the first study to investigate the longitudinal relationship between clinical depression and the metabolic syndrome and analyze repeated measurements of depression, the metabolic syndrome, and central adiposity across time. Thus, it is important to keep in mind that, while several studies have addressed questions which were similar to facets of this study, no study is directly comparable to the current investigation in its entirety. Hence, these results should be interpreted as preliminary until future investigations are able to replicate the findings, particularly since many of the reported associations, while consistent with hypotheses, were marginally significant or nonsignificant trends.

4.2.1 Metabolic Syndrome

Most comparable to the current investigation, a report from the Healthy Women Study showed that women who had elevated baseline depressive symptom scores had significantly greater risk (approximately 30%) of developing the metabolic syndrome over the course of a 7-year follow-up period (Raikkonen et al., 2002). This is consistent with our finding that a lifetime history or current diagnosis of

depression at baseline was associated with significantly greater odds of having the metabolic syndrome over time (Figure 3a), and the nonsignificant finding that women with baseline depression were approximately 60% more likely to develop the metabolic syndrome over the course of the study. Although the elevated risk in the current investigation was not statistically significant, the hazard ratio was approximately 25% higher than the hazard ratio reported by Raikkonen et al. (2002). Thus, it is possible that the use of a categorical predictor (presence / absence of depression) and the relatively small number of women who developed the metabolic syndrome over the course of the study (n = 38) may have reduced the ability to detect significant differences in incident cases of the metabolic syndrome in the current study. Hence, the risk associated with depression may have reached statistical significance in a sample with a greater incidence rate. Additionally, in contrast to the women from the Healthy Women Study, the current sample of women was ethnically and sociodemographically diverse, it included women with other psychiatric and medical conditions (e.g., diabetes, hypertension), and it did not exclude people based on the use of psychotropic or other medications, making the current sample more representative of the general population. Hence, it is possible that the effect of depression on the risk of developing the metabolic syndrome is stronger or more apparent in a relatively homogeneous sample of healthy women than it is in the general population.

The remaining studies of depression and the metabolic syndrome have been cross-sectional, limiting the ability to make direct comparisons with the current investigation. In the only study of the association of clinical depression with the metabolic syndrome, Kinder et al. (2004) showed that a lifetime history of major depression was associated with greater odds of having the metabolic syndrome in young adult women. In contrast, our results do not provide strong support for a cross-sectional association between clinical depression and the metabolic syndrome in middle-aged women (Figure 2), and they suggest that clinical depression and the metabolic syndrome may not be closely related across time (Figure 5a). As mentioned above, one potential explanation for the differences in findings is that a lifetime history of depression may be more strongly associated with the metabolic syndrome in younger, healthy women as compared to the current sample of middle-aged women who may already have preclinical levels of disease (e.g., hypertension, obesity). Consistent with this possibility, Kinder et al.

showed that the relationship between depression and the metabolic syndrome was marginally stronger in women less than 30 years of age.

Finally, cross-sectional data on depressive symptoms and the metabolic syndrome are mixed. In contrast to the current findings, previous studies have shown that elevated scores on continuous measures of depressive symptoms are associated with the metabolic syndrome in women (Raikkonen et al., 2002) and men (McCaffery et al., 2003). However, results of a third study showed that women who met a clinically relevant cutoff for current depressive symptoms, relative to women who did not meet the cutoff, did not have greater odds of having the metabolic syndrome (Herva, Rasanen et al., 2006). This raises the possibility that the variability in findings across studies may also be attributable to the operationalization of depression (e.g., continuous depressive symptoms, categorical depressive symptoms, clinical diagnosis of major depression), and that the association of depression with the metabolic syndrome may not be uniform across the spectrum of depressive symptomatology. Thus, it is plausible that the "depressed" group in the current study was heterogeneous in terms of the severity, chronicity, and presentation of depression, and the variability within the "depressed" and the "non-depressed" groups may have obscured potentially meaningful concurrent associations. Given the nature of the calculations for the GEE models, this may also have implications for the longitudinal analysis of the relationships between depression and the metabolic syndrome across time (Figures 5a), as this analysis treated both depression and the metabolic syndrome as categorical time-varying factors, such that women were able to fluctuate between depression groups (i.e., "depressed" and "not depressed") as well as metabolic syndrome groups (i.e., "metabolic syndrome present" and "metabolic syndrome absent"). Alternatively, the lack of an association between concurrent measures of depression and the metabolic syndrome across time in the current study may suggest that depressive episodes and the metabolic syndrome do not "track" together over time; that is, fluctuations in depression may not be associated with fluctuations in the metabolic syndrome. Consistent with this possibility, Raikkonen et al. (2002) showed that individual changes in depressive symptoms from baseline to follow-up were not related to risk of developing the metabolic syndrome over time.

4.2.2 Central Adiposity and Insulin Resistance

Only four studies have used a longitudinal design to examine the association between depression and central adiposity over time. Consistent with the pattern of results in the current study (Figure 7), Nelson et al. (1999) found that elevated baseline scores on a continuous measure of depressive symptoms predicted significantly greater mean WHR 5-7 years later in middle-aged White women, suggesting that depression may predict greater subsequent central adiposity over an extended period of time. However, the only longitudinal investigation of clinical depression and central adiposity showed no differences between patients with current major depression and healthy controls in the amount of VAT at baseline or one year later (Weber-Hamann et al., 2006). Interestingly, results of analyses conducted with the patients stratified by baseline levels of free cortisol showed that "normocortisolemic" patients, but not "hypercortisolemic" patients, had a marginally greater percent increase in VAT, although there were no differences between depressed patients in general and controls.

The remaining longitudinal reports of depression and central adiposity examined changes in depressive symptoms and central adiposity over time; these analyses are most comparable to the current longitudinal model of the associations between time-varying measures of depression and waist circumference at each visit (Figure 8a). Results of the first study, conducted with middle-aged White diabetic men and women, showed that changes in depressive symptoms from baseline to the 2-year follow-up were positively associated with changes in WHR (Lloyd et al., 1996). On the contrary, in another report from the Healthy Women Study, Raikkonen, Matthews, & Kuller (1999) showed no association between changes in depressive symptoms and changes in WC across an 8-year follow-up ("within-subject" effect); however, women with greater overall WC across time, relative to women with smaller overall WC, reported more symptoms of depression across the follow-up period ("between-subjects" effect). These results are in contrast to the findings of the current study, which showed an inverse association between depression and waist circumference across time (Figure 8a). Together, results of the longitudinal and cross-sectional studies, along with the results of the current investigation, suggest several potential explanations for the variation in findings. More specifically, it is possible that the "short-term" and "longer-term" effects of depression on central adiposity differ, or that depression may

influence subsequent changes in central adiposity over time, but this effect may not be apparent when one only examines absolute levels. Finally, the previously described heterogeneity in depression (e.g., differences in depression presentation or differences in physiological aberrations) may also affect the association between depression and central adiposity.

To explore the possibility that variability within the depression group may influence the overall associations between depression and waist circumference, a "chronicity" variable was created based on the number of depressive episodes from lifetime through visit 05 (0 = no episodes, 1 = a single episode, 2 = more than 1 episode), and univariate GLM was used to compare the mean waist circumference at visit 05 between these three groups. Results showed that women with more than one depressive episode had significantly greater mean waist circumference than women with one or no depressive episodes (results not shown). To further explore the variability in waist circumference within the "depressed" group, another variable was created based on the total number of episodes from lifetime – visit 05 (range 0-6), and univariate GLM was used to compare the mean waist circumference at visit 05 between these seven groups. Although the main effect of the depression group was not significant, examination of group means showed that women with 3 and 5 depressive episodes had the greatest mean waist circumference at visit 05, while women with 6 depressive episodes actually had the lowest mean waist circumference at visit 05, suggesting that the relationship between the number of depressive episodes and waist circumference may not be linear in this sample (see Appendix C, Table 1); however, this should be interpreted with caution as the main effect was not significant. Nevertheless, the considerable variability in mean waist circumference among women who would have fallen into the "depression" category may be another potential explanation for the inverse association between depression and waist circumference across time.

Data from most cross-sectional investigations of clinically depressed young adults suggest that individuals with depression have greater levels of central or visceral adiposity than healthy controls (Eskandari et al., 2005; Kahl et al., 2005; Miller et al., 2003; Thakore et al., 1997), and elevated scores on continuous measures of depressive symptoms are associated with greater central adiposity in women and men (Ahlberg et al., 2002; Haukkala & Uutela, 2000; Katz et al., 2000; Lee et al., 2005; Petrlova et al., 2004; Wing et al., 1991), although null findings have been reported (Cota et al., 2001; Hach et al.,

2006; Herva, Laitinen et al., 2006; Marniemi et al., 2002). Notably, although Weber-Hamann (2002) showed no significant differences between depressed patients overall and controls in mean levels of VAT, "hypercortisolemic" depressed patients had significantly greater levels of VAT than "normocortisolemic" patients but not controls, and "normocortisolemic" patients had significantly lower levels of VAT than controls. In concert with the previously reported findings of Weber-Hamann (2006), these results highlight differences in HPA functioning among depressed patients and suggest that these physiological differences may influence the relationship of depression with the metabolic syndrome and central adiposity.

Finally, previous cross-sectional research on depression and various proxies for insulin resistance or glucose intolerance has shown that clinical samples of depressed patients exhibit more metabolic impairment than healthy and psychiatric controls, and scores on continuous measures of depressive symptoms are associated with indicators of impaired glucose tolerance in White men (Ahlberg et al., 2002; Raikkonen et al., 1994) but not women (Huerta et al., 1995). Results of cross-sectional studies of more direct measures of insulin resistance are mixed. While one study demonstrated an association with depressive symptoms in young adult men (Timonen et al., 2006), another found an association in young adult women but not men (Suarez, 2006). The only study of clinical depression showed that young women with comorbid major depression and borderline personality disorder, but not women with major depression alone, had more insulin resistance than healthy controls (Kahl et al., 2005). Finally, the only longitudinal investigation of depression and insulin resistance showed that baseline levels of depressive symptoms predicted greater HOMA-IR values at baseline; however, baseline depressive symptoms were not independently associated with changes in HOMA-IR values across time (Everson-Rose et al., 2004). Although the literature provides mixed evidence for an association of depression with insulin resistance, the current investigation did not show an association between clinical depression and insulin resistance at baseline or over time in this sample. Post-hoc analyses showed that this null finding was not due to baseline antidepressant use, baseline BMI, or baseline WC (results not shown). As previously discussed, differences across studies may be attributable to differences in the measurement of depression and insulin resistance, sample demographics, and variability in depression as a construct.

4.2.3 Health Behaviors

There is some evidence to suggest that the metabolic syndrome is associated with unhealthy behaviors (Park et al., 2003), and that lifestyle behaviors may link psychological characteristics and components of the metabolic syndrome (Everson-Rose et al., 2004; Scherwitz et al., 1992). Consistent with previous data (Raikkonen, Matthews, & Kuller, 1999), physical activity in this study did not account for the association between depression and waist circumference. However, there was some indication that the effect of depression on the development of the metabolic syndrome was particularly strong in women with low baseline levels of physical activity. It is plausible that physical activity may protect against the effect of depression on the metabolic syndrome or, alternatively, that low levels of physical activity may be a marker of more severe depression or metabolic dysregulation. Consistent with previous research showing that smoking does not influence the association between depressive symptoms and central adiposity (Lee et al., 2005; Nelson et al., 1999; Raikkonen, Matthews, & Kuller, 1999), our results suggest that, while smoking may be associated with a lower waist circumference at baseline, it does influence the association of depression with central adiposity. Together, these findings suggest that physical activity and, to a lesser extent, dietary intake, may affect the development of the metabolic syndrome and central adiposity. However, they provide little support for lifestyle factors as a link between depression and the metabolic syndrome or its components in middle-aged women.

4.3 SUMMARY OF STUDY STRENGTHS AND LIMITATIONS

As highlighted throughout this paper, this study has several significant strengths. Most importantly, it is the first investigation to longitudinally examine the relationship between a clinical diagnosis of depression and the metabolic syndrome across time. In addition, this is the first study to examine the development of the metabolic syndrome over time as a function of baseline depression, to explore whether depression increases risk of developing the metabolic syndrome over time, and to investigate repeated measurements of depression, the metabolic syndrome, and central adiposity across time. Moreover, this is the first study to examine the effects of health behaviors on the longitudinal association between clinical

depression and the metabolic syndrome and investigate whether relationships between depression and the metabolic syndrome or central adiposity are independent of other psychiatric diagnoses. Another strength of the current study is the use of a community-based, representative sample of middle-aged Black and White women undergoing the menopausal transition. Few studies have investigated the association of depression with the metabolic syndrome or central adiposity in middle-aged women, despite evidence to suggest that risk of developing the metabolic syndrome and elevated central adiposity increases with age and may become particularly salient as women move through the menopausal transition (Carr et al., 2004).

Nevertheless, this study has some notable limitations. First, although the use of a diverse, community-based sample of middle-aged women increases the generalizability of the current findings, a potential disadvantage of this sample is that there are many variables which could influence the relationships of interest. While an attempt was made to control for the potential "noise" of other factors, it is plausible that the heterogeneity within the sample as a whole may have obscured or altered associations of depression with the metabolic syndrome, central adiposity, and insulin resistance. In addition, the age and gender of the current sample limits the application of the findings to men and younger populations. A second limitation of the current investigation is that relatively few women developed the metabolic syndrome over the course of the study, possibly reducing the power to detect potentially significant effects of depression on the risk of developing the metabolic syndrome. Similarly, while it is important to examine major depression as a clinical diagnosis, the use of a dichotomous predictor may have less statistical power to detect significant associations than continuous or ordinal variables, particularly if there is a dose-response or non-linear association. As previously discussed, the heterogeneity among individuals diagnosed with depression (e.g., differences in number of episodes, types of symptoms, duration of episodes) may have obscured associations between depression, the metabolic syndrome, and central adiposity, particularly if the associations vary between these characteristics. The use of a dichotomous indicator of depression, particularly as a time-varying predictor, may not have captured this potentially informative diversity. Finally, the likelihood of committing a Type I error across all models may have increased as a function of the number of statistical tests performed.

4.4 BIOLOGICAL PLAUSIBILITY

As presented in Figure 1, the primary candidates for mediating biological pathways are dysregulation of the hypothalamic pituitary adrenal (HPA) axis and the sympathetic adrenal medullary (SAM) system, although there is also some preliminary evidence for a role of aberrant serotonergic functioning. The HPA axis is implicated in the development and exacerbation of abdominal, visceral fat deposition and the metabolic syndrome through a variety of pathways (Surwit et al., 2002), and individuals with excess central or visceral adiposity exhibit HPA hypersensitivity and dysregulation (Philip & Facchini, 1995), frequently elevated levels of cortisol (Tanaka et al., 2004), and failure to habituate cortisol responses to stress (Miller, T. Q. et al., 1996). Numerous studies have found indications of HPA hyperactivity in depressed patients (for review, see Park et al., 2003), and the behavioral symptoms of acute episodes of depression, including psychomotor alterations and decreased appetite, are purported to reflect elevated levels of corticotrophin-releasing hormone (CRH) (Gold & Chrousos, 1999; Gold & Chrousos, 2002). Interestingly, recent studies have highlighted the variability in HPA functioning among depressed patients, particularly between patients presenting with “melancholic” or “atypical” symptoms (Gold & Chrousos, 1999; Gold & Chrousos, 2002), suggesting that the presentation of HPA “dysregulation” may differ among patients with major depression. This is consistent with the findings of Weber-Hamann et al. (2002; 2006) and the hypothesis that variability within the depressed and non-depressed groups in the current study, perhaps in the associated HPA dysregulation, may have affected the associations between depression and waist circumference across time (Figures 8a & 8b). In addition, there is some evidence that HPA alterations may not completely improve upon recovery from a depressive episode (Bhagwagar, Hafizi, & Cowen, 2003), and the remaining dysregulation may be a marker of or a risk factor for relapse (Appelhof et al., 2006). In the longer term, this HPA overactivity may contribute to increased central fat distribution and the development of the metabolic syndrome (Bjorntorp & Rosmond, 1999, 2000a, 2000b). Thus, it is plausible that the inverse association between depression and central adiposity in the current investigation reflects the “acute” effects of HPA dysregulation, whereas the trend for an effect of baseline depression on greater central adiposity over time may reflect the more “long-term” effect of this

dysregulation. Alternatively, it is possible that certain types or characteristics of depression have more aberrant HPA functioning than others.

Activation of the SAM system is also known to affect visceral fat deposition. Catecholamines stimulate lipolysis and free fatty acid (FFA) mobilization, particularly in visceral fat cells (Roux, Jacobs, & Kiefe, 2002), reflected, for example, in the increased urinary catecholamine metabolite excretion exhibited by individuals with high central adiposity (Rebuffe-Scrive, Walsh, McEwen, & Rodin, 1992). Given the evidence for autonomic dysregulation in depression (Carney, Freedland, & Veith, 2005), it is plausible that SAM activity may be a mechanism linking psychological factors with the metabolic syndrome. Finally, there is preliminary evidence to suggest that the metabolic syndrome and central adiposity may be associated with altered serotonergic functioning (Muldoon, et al., 2006; Muldoon et al., 2004; Rosmond, Bouchard, & Bjorntorp, 2002). Aberrations such as decreased CSF concentrations of serotonin metabolites, decreased serotonin uptake and transporter binding, blunted neuroendocrine responses to serotonergic stimuli, and alterations in the density of serotonin receptors have all been demonstrated in individuals with depression, and alterations may remain even upon recovery from acute depressive episodes (for reviews, see Mann, 1999; Owens & Nemeroff, 1994; Stockmeier, 2003).

4.5 STUDY IMPLICATIONS AND FUTURE DIRECTIONS

The findings of the current investigation provide preliminary support for clinical depression as a predictor of increased risk for the metabolic syndrome. Namely, the results of this study provide some preliminary evidence that women with a lifetime history or current diagnosis of major depression may be at greater risk of having and developing the metabolic syndrome over time (Figures 3 and 4). In contrast, the results suggest that major depression overall may not be concurrently related to the metabolic syndrome and that depression “status” and the metabolic syndrome may not “track” together over time (Figures 2 & 5). This raises the possibility that there may be underlying physiological ramifications of depression which, over time, adversely affect metabolic processes and increase risk of developing the metabolic syndrome. However, given the relatively small number of women who developed the metabolic syndrome over the course of the investigation, more research is needed to replicate these findings before

drawing any definitive conclusions. Importantly, the current findings suggest that cross-sectional studies of depression and the metabolic syndrome may not necessarily capture the "true" relationship between these variables, highlighting the need for future prospective investigations of the relationship between clinical depression and the metabolic syndrome.

Similarly, the current findings suggest that concurrent and longitudinal associations of clinical depression with central adiposity may differ. More specifically, depressive episodes may be concurrently associated with lower waist circumference across time (Figure 8a), possibly reflecting a reduction in appetite and subsequent weight loss. However, depression may adversely affect the development of central adiposity at a later point in time (Figures 7), consistent with the long-term effects of chronic HPA dysregulation or serotonergic dysfunction on body fat distribution. Nevertheless, it is possible that these findings reflect differences among women in the individual associations between depression and waist circumference across time. Although these findings should be considered preliminary, they underscore the potential importance of distinguishing short-term or concurrent associations between depression and central adiposity from prospective relationships.

This study also raises the possibility that the relationship between depression, the metabolic syndrome, and central adiposity may not be uniform among individuals with depression. This presents important questions about our conceptualization of depression and its association with the metabolic syndrome which may have implications for integrating results from studies of depressive symptoms with investigations of major depression. While these questions are beyond the scope of this study, future research could address these questions in several ways. For example, studies could examine the effect of the chronicity of depression on the metabolic syndrome by comparing groups according to the number of depressive episodes or the total amount of time that an individual spends in a depressive episode, with the aim of capturing the effect of long-term exposure to clinical depression. Alternatively, future studies could also examine individual trajectories among patients with depression to underscore the effect of changes in depression on individual changes in the parameters of the metabolic syndrome. Another avenue for future research is to examine whether there are differences between depressive subtypes (e.g., melancholia, atypical depression) or levels of "severity" (e.g., major, subthreshold), and whether

there are differences between individuals who meet diagnostic criteria for a depressive disorder and those who endorse depressive symptoms.

Results of the current study suggest that diet, physical activity, and smoking may not directly link clinical depression with risk of the metabolic syndrome, although future studies are needed to confirm this possibility. Nonetheless, the question of how depression is related to the metabolic syndrome remains. In particular, this study did not examine whether the physiological aberrations presented on the left side of Figure 1 (e.g., hypothalamic, sympathetic, or serotonergic dysregulation) are pathways by which depression may affect risk for the metabolic syndrome. Thus, future investigations should incorporate indicators of plausible biological mediators as well as health behaviors, and examine whether there are independent pathways or whether there is an underlying transactional process between health behaviors and physiological dysregulation. Future research may also aim to explore whether common genetic factors or other common vulnerabilities (e.g., early traumatic experiences) link depression with the metabolic syndrome.

Given the effect of antidepressant use on the association of depression with the metabolic syndrome and central adiposity in the current investigation, future investigations of the effect of antidepressant treatment on the association of depression with the metabolic syndrome and central adiposity are warranted. More specifically, future studies should explore whether antidepressants are a pathway linking depression with the metabolic syndrome, a moderator of this association, or simply a marker depression (and possibly its severity or chronicity). While there is some evidence to suggest that treatment with serotonergic agents decreases visceral fat deposition (Van Gal, Wauters, Peiffer, & De Leeuw, 1998), the data are not entirely consistent (Ljung et al., 2001). Available literature suggests that the effect of antidepressants on body weight and appetite is dependent upon the type of antidepressant as well as the duration of antidepressant use, such that some antidepressants appear to be associated with weight gain, while others are associated with weight loss or no change in weight (for review, see Zimmerman, Kraus, Himmerich, Schuld, & Pollmacher, 2003). Unfortunately, the current study did not have complete data on the specific types of antidepressants used at each visit, precluding a more detailed investigation of the effect of antidepressants on the associations between depression, the metabolic syndrome, and central adiposity.

This study also highlights the importance of examining these questions in samples of men and women who are representative of the general population. While the current study is a step toward a better understanding of the relationship between clinical depression and the metabolic syndrome in women, future studies are needed replicate these findings in diverse samples of women and men. In addition, given the fairly high prevalence of precursors of the metabolic syndrome in children and adolescents (Goodman, Daniels, Morrison, Huang, & Dolan, 2004), investigations of the potential effect of depression in younger populations are warranted.

If future research does establish a prospective link between depression and the metabolic syndrome, the next step is to experimentally test the hypothesis that depression is causally related to the metabolic syndrome. One potential avenue for future work is to develop a trial of psychological interventions for depression (e.g. cognitive-behavioral therapy, interpersonal therapy) and follow its effects on the development, exacerbation, or remediation of the metabolic syndrome. Alternatively, trials that intervene on the metabolic parameters (e.g. decreasing visceral adiposity through surgery, treating insulin resistance with pharmacotherapy, altering body fat distribution with lifestyle interventions) could be used to evaluate their effect on depression. Only through these experimental manipulations will we be able to elucidate the true nature of the relationship between depression and the metabolic syndrome.

Implications of this research extend beyond improving our understanding of the development of the metabolic syndrome itself. Depression has long been recognized as significant risk factors for disease, including coronary heart disease and Type 2 diabetes (Musselman et al., 2003), and it may be associated with increased risk for these diseases in part through its association with the development of the metabolic syndrome. However, no study to date has examined this hypothesis, highlighting the need for future investigations of the metabolic syndrome as a pathway linking depression with disease. Nevertheless, these findings suggest that a better understanding of the relationship between depression and the metabolic syndrome may provide a unique opportunity for the prevention and treatment of some of the major causes of morbidity and mortality.

4.6 CONCLUSIONS

Available literature on depression and the metabolic syndrome suggests that depression may be associated with increased central adiposity, insulin resistance, and the metabolic syndrome. While cross-sectional data suggest that depression, particularly depressive symptoms, is associated with increased central adiposity and insulin resistance, longitudinal data are less consistent. The few studies of the metabolic syndrome in its entirety suggest that a history of major depression is cross-sectionally associated with presence of the metabolic syndrome, and depressive symptoms predict increased risk for developing the metabolic syndrome over time, although no study to date has prospectively examined the relationship between clinical depression and the metabolic syndrome. Hence, the purpose of the current study was to investigate the relationship between clinical depression and the metabolic syndrome and its core components of central adiposity and insulin resistance in a community-based sample of middle-aged women over a 6-year period.

Overall, this study provides some preliminary evidence that clinical depression may be related to the metabolic syndrome and central adiposity in Black and White women undergoing the menopausal transition. More specifically, the current findings indicate that women with a lifetime history or current diagnosis of major depression may be at greater risk of having and developing the metabolic syndrome over time. However, the results suggest that major depression overall may not be concurrently related to the metabolic syndrome and that depression “status” and the metabolic syndrome may not “track” together over time. Given the relatively small number of women who developed the metabolic syndrome over the course of the investigation, more research is needed to replicate these findings before drawing any definitive conclusions. Findings of the relationship between depression and central adiposity were similarly dependent upon the nature of the question and the statistical model. Results showed that clinical depression may adversely influence the development of central adiposity at a later point in time, but findings suggest that depression may be inversely associated with concurrent measures of central adiposity across time. It is possible that these findings reflect differences in the “short-term” and “long-term” effect of clinical depression on central adiposity. The current study found no support for an association between clinical depression and insulin resistance in middle-aged women. Importantly, the current findings, while preliminary, suggest that cross-sectional studies of depression and the metabolic

syndrome may not necessarily capture the “true” relationship between these variables, highlighting the need for future prospective investigations of the relationship between clinical depression, the metabolic syndrome, and central adiposity. In sum, the current study provides preliminary evidence for they hypothesis that major depression may be associated with risk of having the metabolic syndrome and increased central adiposity, suggesting that future investigations of the relationship between clinical depression and the metabolic syndrome are warranted.

APPENDIX A. DEPRESSION DEFINED AS MAJOR DEPRESSION, MINOR DEPRESSION, OR DYSTHYMIA

Table A1: Characteristics of participants with a lifetime history or current major depressive episode at baseline, lifetime history or current minor depressive episode or dysthymia at baseline, and no lifetime history or current depression at baseline

	No lifetime history / no current depression at visit 00 n (%)	Lifetime history / current minor depression or dysthymia visit 00 n (%)	Lifetime history / current major depression at visit 00 n (%)
Number of participants	209	62	150
Major Depressive Episode			
Visit 01 (n = 384)	6 (3.1%)	3 (5.5%)	43 (31.6%)
Visit 02 (n = 386)	7 (3.6%)	4 (7.3%)	41 (29.7%)
Visit 03 (n = 377)	8 (4.3%)	4 (7.5%)	35 (25.5%)
Visit 04 (n = 364)	4 (2.2%)	2 (3.9%)	38 (28.6%)
Visit 05 (n = 353)	6 (3.4%)	4 (8.5%)	38 (29.2%)
Metabolic Syndrome (MS)			
Visit 00	37 (17.7%)	12 (19.4%)	36 (24.0%)
Visit 01	36 (19.5%)	10 (19.2%)	36 (28.1%)
Visit 03	33 (20.1%)	7 (17.9%)	32 (26.9%)
Visit 05	30 (20.5%)	5 (13.2%)	25 (24.5%)
Cumulative MS (00-05)	54 (33.5%)	16 (36.4%)	53 (44.5%)
Incident MS (00-05)	17 (13.7%)	4 (12.5%)	17 (20.5%)

Table A2: Chi-square analyses showing baseline association between lifetime history or current diagnosis of any depression (redefined) and the metabolic syndrome

	Lifetime History or Current Major Depression, Minor Depression, or Dysthymia at visit 00			
Metabolic Syndrome at visit 00	Absent n (%)	Present n (%)	Chi^2 *	*p*-value
Absent	172 (82.3)	164 (77.4)		
Present	37 (17.7)	48 (22.6)		
Total	209	212	1.60	.21

* Chi^2 comparing depression to no depression

Table A3: Logistic regressions showing the association of lifetime history or current diagnosis of any depression predicting cumulative index of the metabolic syndrome at visit 05 (ever from 00 – 05)

DV: Presence of the metabolic syndrome ever from 00 – 05 [1]

	Variable	OR (95% CI)	*p*-value
Univariate (n = 324)			
	Depression	1.45 (0.96, 2.28)	.100
Age and Race (n = 324)			
Step 1:			
	Depression	1.51 (0.96, 2.40)	.077
	Age	1.12 (1.02, 1.22)	.020
	Race	1.66 (1.02, 2.70)	.042
Physical activity score at visit 00 (n = 322)			
Step 2:			
	Depression	1.62 (1.01, 2.60)	.046
	Age	1.12 (1.02, 1.23)	.019
	Race	1.38 (0.83, 2.30)	>.10
	Physical activity	(-) 0.76 (0.66, .88)	<.001
% kcal fat at visit 00 (n = 324)			
Step 2:			
	Depression	1.51 (0.95, 2.40)	.078
	Age	1.12 (1.02, 1.22)	.020
	Race	1.60 (0.98, 2.61)	.061
	% kcal fat	1.03 (0.99, 1.06)	.092
History / current other psychiatric diagnosis at visit 00 (n = 323)			
Step 2:			
	Depression	1.41 (0.87, 2.28)	.161
	Age	1.12 (1.02, 1.23)	.019
	Race	1.58 (0.97, 2.59)	.068
	Alcohol use / abuse	1.77 (0.85, 3.68)	>.10
	Drug use / abuse	1.06 (0.41, 2.74)	>.10
	Any anxiety disorder	(-) 0.86 (0.48, 1.54)	>.10

[1] DV = dependent variable; OR = odds ratio; CI = confidence interval

Table A3: (continued)

DV: Presence of the metabolic syndrome ever from 00 – 05 [1]			
	Variable	OR (95% CI)	*p*-value
Antidepressant use at visit 00 (n = 324)			
Step 2:			
	Depression	1.26 (0.76, 2.08)	.367
	Age	1.12 (1.02, 1.23)	.018
	Race	1.78 (1.08, 2.92)	.023
	Antidepressants	1.90 (0.97, 3.72)	.063
Diabetes at visit 00 (n = 322)			
Step 2:			
	Depression	1.52 (0.93, 2.49)	.092
	Age	1.11 (1.00, 1.22)	.043
	Race	1.53 (0.90, 2.58)	> .10
	Diabetes	42.62 (5.64, 322.27)	.000

DV: Incident metabolic syndrome from 01 - 05			
	Variable	OR (95% CI)	*p*-value
Univariate (n = 239)			
	Depression	1.41 (0.70, 2.82)	.338
Age and Race (n = 239)			
Step 1:			
	Depression	1.48 (0.73, 3.00)	.273
	Age	1.08 (0.94, 1.24)	>.10
	Race	1.43 (0.68, 3.02)	>.10

[1] DV = dependent variable; OR = odds ratio; CI = confidence interval

APPENDIX B. DEPRESSION DEFINED AS MAJOR DEPRESSION OR ANTIDEPRESSANT USE

Table B1: Chi-square analyses showing baseline association between lifetime history / current diagnosis of major depression or lifetime history / current use of antidepressants and presence of the metabolic syndrome

	Lifetime history / current major depression at visit 00 or lifetime history / current antidepressant use at visit 00			
Metabolic Syndrome at visit 00	Absent n (%)	Present n (%)	Chi^2 *	*p*-value
Absent	211 (82.3)	125 (75.8)		
Present	45 (17.6)	40 (24.2)		
Total	256	165	2.77	.096

* Chi^2 comparing depression to no depression

Table B2: Logistic regressions showing the association of baseline major depression (lifetime history / current) or antidepressant use (lifetime history / current) predicting cumulative index of the metabolic syndrome at visit 05 (ever from 00 – 05)

DV: Presence of the metabolic syndrome ever from 00 – 05 [1]			
	Variable	OR (95% CI)	*p*-value
Univariate (n = 324)			
Step 1:			
	Depression or antidepressant use	1.65 (1.05, 2.61)	.031
Age and Race (n = 324)			
Step 1:			
	Depression or antidepressant use	1.74 (1.09, 2.78)	.019
	Age	1.12 (1.02, 1.22)	.020
	Race	1.71 (1.04, 2.79)	.033
DV: Incident metabolic syndrome from 01 – 05			
	Variable	OR (95% CI)	*p*-value
Univariate (n = 239)			
Step 1:			
	Depression or antidepressant use	1.79 (0.89, 3.60)	.102
Age and Race (n = 239)			
Step 1:			
	Depression or antidepressant use	1.88 (0.93, 3.82)	.079
	Age	1.09 (0.95, 1.24)	>.10
	Race	1.46 (0.69, 3.08)	>.10

[1] DV = dependent variable; OR = odds ratio; CI = confidence interval

Table B3. Cox proportional hazard model of the association between baseline major depression or antidepressant use (lifetime history / current) and risk of developing the metabolic syndrome through visit 05

Model (n = 336)	Predictor Variable	Hazard Ratio (95% CI) [1,2]	*p*-value
1	Lifetime history / current MD or use of antidepressants at visit 00	1.73 (0.91, 3.26)	0.092
2	Lifetime history / current MD or use of antidepressants at visit 00	1.79 (0.94, 3.38)	0.074
	Age at visit 00	1.12 (0.99, 1.26)	0.076
3	Lifetime history / current MD or use of antidepressants at visit 00	1.80 (0.95, 3.42)	0.071
	Age at visit 00	1.12 (0.99, 1.26)	0.073
	Race (Black)	1.13 (0.58, 2.22)	>.10
4	Lifetime history / current MD or use of antidepressants at visit 00	1.82 (0.96, 3.46)	0.067
	Age at visit 00	1.12 (0.99, 1.26)	0.075
	Race (Black)	1.12 (0.57, 2.21)	>.10
	Menopausal Status 0 (early perimenopause)	0.82 (0.43, 1.56)	>.10
6	Lifetime history / current MD or use of antidepressants at visit 00	1.77 (0.94, 3.36)	0.079
	Age at visit 00	1.13 (0.99, 1.28)	0.057
	Race (Black)	0.90 (0.45, 1.81)	>.10
	Physical activity score at visit 00	0.80 (0.66, 0.99)	0.038

[1] CI = confidence interval; MD = major depression

[2] Results of full multivariate model controlling for age, race, menopausal status, and physical activity were similar.

APPENDIX C. WAIST CIRCUMFEENCE AND FREQUENCY OF DEPRESSIVE EPISODES

Table C1. Mean waist circumference at follow-up visit 05 according to number of depressive episodes (major depression or subthreshold recurrence) across study period (00 – 05)

Total number of depressive episodes	Number of participants	Waist circumference at visit 05 Mean (SD) [1]
0	177	88.72 (14.83)
1	55	88.17 (13.98)
2	33	91.72 (19.90)
3	24	95.43 (19.12)
4	13	93.45 (10.15)
5	8	100.63 (16.75)
6	3	87.60 (7.52)

[1] SD = standard deviation

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FOOTNOTES

[1]Analyses for the metabolic syndrome were also conducted with diabetes defined only according to self-reported use of “insulin or pills for sugar in her blood”. There were no differences in results when diabetes was defined in this manner.

[2]Standardized Pearson residuals were calculated and graphed to identify potential outliers in the data (Hardin & Hilbe, 2003; Rabe-Hesketh & Everitt, 2004). Analyses were then rerun excluding participants with Pearson residuals greater than 4 (n=1) and subjects with the most extreme values of WC (top 2%). Results of these analyses did not differ from those described with the full sample. Plots of residuals against predicted scores of WC showed no violations of normality, heteroscedasticity, or nonlinearity (Hardin & Hilbe, 2003; Rabe-Hesketh & Everitt, 2004). Sensitivity analyses were run with the 264 women with complete data for depression and WC at every visit to explore the potential effect of missing data on the above model; the negative association between depression and WC remained significant ($p < .01$).