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ASSOCIATION BETWEEN CHILDHOOD MALTREATMENT AND TYPE 2 DIABETES MELLITUS: A RETROSPECTIVE COHORT STUDY IN THE UNITED STATES

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A RETROSPECTIVE COHORT STUDY IN THE UNITED STATES

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Diep Poulos BS MS
2019

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by

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ASSOCIATION BETWEEN CHILDHOOD MALTREATMENT AND TYPE 2 DIABETES

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This retrospective cohort study analyzed self-reported and biological data collected from MIDUS in 2004-2006 to understand the association between the types of childhood maltreatment (CM) and Type 2 Diabetes Mellitus (T2DM). The central hypothesis of this study is that childhood maltreatment is positively associated with adult onset diabetes (T2DM). CM has been associated with lifelong morbidity and an increased risk in chronic diseases such as diabetes and heart disease (Bernstein RE, 2013).

In this study, CM was defined by the Childhood Trauma Questionnaire (CTQ). The CTQ has three types of abuse: physical, sexual, emotional, and two types of neglect: physical and emotional. Within each type of CM, there were four severity status: minimal/none, moderate, heavy, and severe. The variables analyzed were demographics: age, sex, highest educational attainment, and race, depression status, obesity status, and CM. This research found a 1.25 times increase in risk for high HbA1C for exposed participants compared to unexposed. The results of this study support the initial hypothesis that CM is significantly associated with T2DM. The findings of this study are similar to previous knowledge and biological plausibility. This study concluded that CM is positively associated with an increase in CM even when obesity and depression status are held constant.

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BACKGROUND

Childhood maltreatment affects approximately 1 in 7 children yearly (CDC, 2019). In 2012, there was an estimated 3.4 million referrals of children abused or neglected. Among them, 78% were victims of neglect (Fang X, 2012). The other children were victims of the following maltreatments: 18% from physical abuse, 9% from sexual abuse, and 11% from other forms of maltreatment such as emotional abuse (Fang X, 2012). However, these values may be an underestimation of the true numbers (Finkelhor D, 2015). Finkelhor et al. approximated 1 in 4 U.S. children experience some form of CM in their life (CDC, 2019) (Finkelhor D, 2015). CM victims are not only affected by abuse and neglect, but they also suffer lifelong morbidity (Bernstein RE, 2013).

Physiology of childhood stressors.

Human stress response consist of two systems: the hypothalamic-pituitary-adrenal axis (HPA) and the sympathetic nervous system (SNS) (Smith SM, 2006). The HPA system regulates chronic stress while SNS regulates acute stressors. SNS is the body's "fight or flight" response. In response to stress, the HPA system releases adrenocorticotrophic hormone (ACTH), which interacts with the adrenal cortex. The adrenal cortex responds to the interaction by the production of cortisol, a form of glucocorticoid (Hornor, 2015). Exposure to chronic stress in childhood causes HPA dysregulation across biological systems, including the immune, metabolic, and nervous systems (Hornor, 2015). This HPA dysregulation results in the excess circulation of cortisol (hypercortisolemia), which affects its ability to lower blood glucose levels (hyperglycemia). Excess cortisol secretion has been associated with an increased risk of Type 2 Diabetes Mellitus (T2DM) (Shonkoff JP, 2009).

CM on obesity and depression.

Physical and emotional stressors during intrauterine life, adolescence, and childhood have been associated with an increased risk of developing chronic illnesses as adults (Barker DJP, 2005). Research by Barker et al. determined individuals with low body mass index (BMI) at ages 2 years old and increased BMI at ages 2 through 11 were at an increased risk for coronary disease as adults. Each standard deviation decrease in BMI at two years old resulted in a 24% increase risk for coronary disease as adults. The hazard ratio associated with 1 standard deviation ($p < 0.05$) increase in BMI was 0.76 with 95% CI: (0.66, 0.87) for boys and 0.62 95% CI: (0.46, 0.82) for girls. Barker et al. proposed the biological plausibility for the association was due to rapid growth during childhood. In 2016, a retrospective cohort study found significant ($p < 0.5$) synergistic interaction between depression and obesity (Tsenkova VK, 2016). Many obese individuals do not develop diabetes. This research provides the rationale for psychological risk factors, such as childhood maltreatment, as a risk factor for diabetes.

T2DM and CM.

T2DM is characterized by insulin resistance and inadequate insulin secretion by the pancreatic β -cells (Ravish, 2015). Insulin resistance is caused by several mechanisms. One of them is the pro-inflammatory cytokines (messenger proteins) in plasma (Ravish, 2015). These cytokines can be detected using high sensitivity C-reactive protein (hsCRP). HsCRP is released into the blood by the liver during inflammation and has been used as a biomarker for T2DM (Ravish, 2015). A prospective cohort study determined that individuals with a history of childhood maltreatment were more likely to have a higher hsCRP level than controls $p < 0.05$

and $RR=2.07$ 95% CI: (1.23, 3.47) (Danese, 2008). This study also analyzed the association between the hsCRP level for currently depressed individuals but did not find a significant association in risk, $RR=1.40$ with 95% CI: (0.97, 2.01). This study demonstrated individuals with a history of CM continue to show signs of systemic inflammation into adulthood regardless of the current depressive state. As previously stated, chronic inflammation can cause insulin resistance, as seen in T2DM. In summary, current available research are mixed.

Public Health Significance

The immediate impact of this research will fill the gap in knowledge of the association between CM and T2DM. This research will analyze five factors of childhood maltreatment with severity status and their possible association in the development of T2DM. It may be possible that different types of childhood trauma will affect T2DM differently. A potential impact is that increased knowledge of the association between CM and T2DM will provide a narrower scope of focus for further longitudinal studies.

Hypothesis, Research Question, Specific Aims or Objectives

AIM: Determine the association between childhood maltreatment and the manifestation of type 2 diabetes mellitus in adults.

This aim will be achieved by conducting a retrospective cohort study using secondary data collected from the Midlife in the United States (MIDUS) Study. MIDUS is an ongoing longitudinal cohort study that collects data on over 7,000 U.S. residents. Childhood maltreatment status is classified into 5 subgroups: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. Minimization/denial scores were also reported

in order to determine if underreporting occurred. T2DM will be defined as HbA1C level. Multiple linear regression will be used to analyze the associations between CM and T2DM.

The expected outcome will be increased knowledge of the association between childhood maltreatment and diabetes. The immediate impact will be an increase in knowledge of how CM affects T2DM. An increase in knowledge will provide the rationale for further longitudinal studies on CM and its effects on T2DM.

METHODS

Study Design

Parent Study-MIDUS. This present study used secondary data from the Midlife in the United States (MIDUS) Study. MIDUS is a longitudinal study covering multiple disciplines in health, including physical and psychological health. The MIDUS study is ongoing, and it is separated into four waves: MIDUS I (M1), MIDUS II (M2), Refresher (MR), and MIDUS III (M3). Each MIDUS wave was further categorized into separate projects. M1 contains two projects: Survey and Daily Diary. In addition to the first two projects, M2 had four additional projects: Cognitive, Biomarkers, Neuroscience, and the Milwaukee Survey. This present study used data collected from the M1 Survey for baseline data, the M2 Survey for exposure status, and the M2 Biomarkers for the outcome status. The M1 Survey data were collected during 1995-1996, the M2 Survey data were collected in early 2004, and the M2 Biomarker Project data were collected in late 2004.

Current study. To establish temporality and determine risk of Type 2 Diabetes Mellitus (T2DM), this study followed a retrospective cohort design.

Possible confounders were age, sex, race, education level, depression and obesity. Confounder status will be determined at M2 Survey. Exposure status was determined through data collected in the M2 Survey as the M1 Survey did not contain questions on childhood maltreatment. Due to the nature of childhood maltreatment, this exposure would have occurred prior to the M2 Biomarker data collection. Outcome status, HbA1c level, was determined through data collected from the M2 Biomarker Project.

Study Subjects

Not used in this study is the initial data collection, M1 Survey (1994), for the parent study. Eligible participants for M1 were English-speaking noninstitutionalized residents ages 25-74 from the continental United States. The M1 study subjects were selected using random digit dialing. There were a total of 4,244 M1 participants. The follow-up data collection on the M1 participants began in 2004. Out of 4,244 M1 participants, 2,746 participants responded to the follow-up. Of these 2,746 participants, 80% completed the M2 Survey. The M2 Biomarkers participants were selected from the M2 Survey sample by random digit dialing. There were 1,255 participants in the M2 Biomarkers Project.

Sample Size Calculation and/or Study Power

At 80% power and a significance level of 0.05, this study has the ability to determine an effect size of 0.0397 increase in HbA1C for the exposure of physical abuse. Similarly, this study can detect an effect size of 0.024 increase in HbA1C for the exposure emotional neglect and 0.035 for emotional abuse.

Data Collection

The M2 Survey and Biomarker Project data collection began in 2004. The participants traveled to one of three clinical research centers (GCF) for an overnight stay. The three GCF sites included: 1) University of California, Los Angeles, 2) University of Wisconsin, and 3) Georgetown University. Participants were assigned to one of three sites based on their region of residence: West Coast, Midwest, or East Coast. A Manual of Operating Procedures (MOP) was used at all three facilities to ensure consistency. The participants were required to complete the M2 Self-Administered Questionnaire (SAQ) on day one of two. The M2 SAQ was a 25-page booklet with documentation on the Childhood Trauma Questionnaire (CTQ) and over 15 other scales. Urine and blood were collected on day two after a 12-hour fast (Dienberg, 2010).

Laboratory methods. All the urine and blood samples collected were processed at individual facilities and shipped to the MIDUS Biocare Lab for assay in order to maintain consistency. Frozen samples were stored in a -60 C to -80 C freezer until shipment. HbA1c samples were sent weekly, and frozen urine samples were sent monthly (Dienberg, 2010). The detailed collection protocol for the Biomarkers Project can be found at the MIDUS website (Midlife in the United States -MIDUS 2, 2004-2009).

Data Analysis

Statistical Analysis. Multiple linear regression was used to determine the association between CM and T2DM. All statistical analysis was conducted through STATA 16.

Data cleaning. The preliminary analysis of continuous variables using scatterplots and boxplots was used to determine any potential outliers. The descriptive summary can be reviewed from Table 1. Demographic covariates include age, sex, highest educational attainment, and race. The demographic covariates in this study are summarized in Table 1.

Outcome variable. The T2DM status was determined by data collected as part of the M2 Biomarkers Project. The major complication in this study was the study power as the prevalence for both exposure and unexposed group was small. For this reason HbA1C was kept as a continuous variable. Individuals who were diagnosed with diabetes within the last 12 months of data collection were adjusted for in the final models.

Exposure variable. The Childhood Trauma Questionnaire (CTQ) separates childhood abuse into 5 categories: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. The sixth variable from the CTQ, minimization/denial, was used as an indicator for underreporting. The scores range from 1 (no minimization) to 3 (high minimization). As set by the CTQ manual, the minimization score was coded as 0 if participants scored a 1 or 2, and 1 if the minimization score was equal to 3. Structure and reliability testing found the CTQ to be a valid measure of abuse and neglect (Paivio SC, 2004). Table 2 contains exposure status and cut-off scores based on the CTQ manual (MacDonald, 2016).

Confounders. Based on the literature review, one potential confounder is depression status. The depression status will be determined through the data collected as part of the M2 Survey. The depression status was measured using the CES-D Scale. Depression is defined as scoring ≥ 16 on the CES-D Scale. This cutoff criteria has a sensitivity of 0.807 and a specificity of 0.717 when tested in a non-hospital or nursing home environment. The 20-question scale has been validated as to having high internal consistency, acceptable test-retest stability, and substantial evidence of construct validity. These properties hold across population subgroups and sexes (LS, 1977). The second common confounder reported in literature is the obesity status due to its possible role as a mediator for T2DM. In this study, obesity was explored as a possible secondary outcome in addition to a confounder. Obesity was determined by the waist-to-hip (W: H) ratio calculation. Generally, obesity status is determined through body mass index (BMI), waist circumference (WC), and waist to hip ratio (W: H). To determine a more accurate diabetes screening measurement, a study by (Balkau, 2005) tested all three methods (Balkau, 2005) found W: H ratio measures have higher sensitivity over WC and BMI (Balkau, 2005) . The cut-off point for all three methods varies with population. A meta-analysis by (Qiao, 2009) determined the most accurate cut-off W: H ratio for Caucasian residents in the United States was 0.96 for men and 0.91 for women. This race distribution was reflected in the present study's sample population. The cut-off point had a sensitivity and (specificity) of 0.69 (0.58) for males and 0.69 (0.64) for females, respectively. The cut-off point was determined specifically to assess type 2 diabetes risks (Qiao, 2009).

Human Subjects Considerations

This study has been exempt by CPHS. IRB Number: HSC-SPH-19-0690

RESULTS

Table 1: Demographic & Summary Statistics

Continuous Variables			
Variable	Mean	Standard Deviation	Range
Age	54.600	11.700	34-84
Waist-to-Hip Ratio	0.895	0.624	1.720
Overall Depression Score	8.680	8.080	0-54
HbA1C	6.094	1.156	3.8-19.662
Categorical Variables			
Variable	N (%)	Variable	N (%)
Sex		¹ Depression Status	
Male	536 (43.72)	Yes	216 (17.62)
Females	690 (56.28)	No	1010 (82.38)
² Obesity		Unexposed & Depression	
Male	281 (52.43)	Depressed	202 (16.48)
Female	135 (19.57)	Not Depressed	1,024 (83.52)
Educational Attainment		Race	
Less than High School	741 (60.44)	Caucasian	961 (78.38)
More than High School	483 (39.40)	Non-Caucasian	265 (21.62)

¹ CESD cut off ≥ 16

² WHR cut-off male ≥ 0.96 , female ≥ 0.91

Table 2: Types of CM Cut-off scores

Types of CM	Emotional Abuse	Physical Abuse	Sexual Abuse	Emotional Neglect	Physical Neglect
Minimum	³ ≤8	≤7	≤5	≤9	≤7
Moderate	>8 and ≤12	>7 and ≤9	>5 and ≤7	>9 and ≤14	>7 and ≤9
Heavy	>12 and ≤15	>9 and ≤12	>7 and ≤12	>15 and ≤17	>9 and ≤12
High	≥16	≥13	>13	≥18	≥13

Table 3: Exposure Summary

Types of CM	Emotional Abuse	Physical Abuse	Sexual Abuse	Emotional Neglect	Physical Neglect
Minimum	837 (20%)	931 (22%)	925 (22%)	679 (16%)	876 (21%)
Moderate	214 (24%)	124 (14%)	84 (9%)	323 (36%)	153 (17%)
Heavy	69 (14%)	84 (18%)	96 (20%)	121 (25%)	108 (23%)
High	92 (21%)	73 (17%)	107 (25%)	89 (20%)	75 (17%)

In order to better interpret the results, demographic covariates, current depressive state, and obesity status were analyzed as a baseline guide for comparison. Table 3 summarizes the baseline results.

³ Cut off points based on CTQ manual

Table 4: Result of Covariates and Outcome.

Variable	Odds Ratio	P-value	95% CI
Age	1.019176	0.000	1.018053; 1.0203
Sex	1.436616	0.000	1.394234; 1.480287
Educational Attainment	.999032	0.668	.9946198; 1.003464
Race	1.084723	0.000	1.040379; 1.130957
Obese (male & female)	1.19208	0.000	1.147007; 1.238925
Current Depressive State	1.148796	0.000	1.097821; 1.202137

Multiple linear regression was completed for each type of CM with ordinal cut-off points as illustrated in Table 2. Age, sex, educational attainment, race, and previous diabetic diagnosis were accounted for in each model. In addition to the demographics, the minimization indicator (0/1) was added to the model. Due to the wide range of HbA1C in the dataset, logHbA1C was used. There was a significant difference in the logHbA1C level for participants who had experienced heavy physical abuse compared to those who had experienced (unexposed) minimal physical abuse. There was a 1.072x increase in mean HbA1c level for individuals with moderate physical abuse, and a 1.078x increase in mean HbA1C level for individuals with heavy physical abuse compared to those with minimal physical abuse (Model A). This association was maintained even after the depression status was introduced to the model. Including depression status, moderate PA exposed participants had a 1.072x increase, and heavy PA had a 1.081x increase in mean HbA1C level compared to unexposed (Model B). Obesity status for both men and women was added in Model C and both moderate and heavy physical abuse levels were

significant. There was a 1.063x increase in HbA1C level for individuals exposed to moderate physical abuse, and a 1.060x increase for individuals exposed to heavy physical abuse. When CM was analyzed as an exposure, without differentiation of types, the relative risk ratio was 1.25 (1.21; 1.28) when obesity and depression status were held constant. Table 4 summarizes the four models.

Table 5: Physical Abuse (PA) & HbA1C

Models	Variables	Risk compared to unexposed	p-value (95% CI)
A	Age, sex, educational attainment, race, physical abuse	Moderate PA: 1.072 Heavy PA: 1.078	0.001 (1.027; 1.119) 0.005 (1.023; 1.137)
B	Model A + depression status	Moderate PA: 1.072 Heavy PA: 1.081	0.001 (1.027; 1.119) 0.004 (1.025; 1.140)
C	Model A + depression status + obesity status	Moderate PA: 1.063 Heavy PA: 1.060	0.004 (1.019; 1.108) 0.029 (1.006; 1.116)
D	Model A + depression status+ obesity+ overall CM exposure	Exposed: 1.25	0.000 (1.212; 1.286)

In addition to physical abuse, both emotional abuse (EA) and emotional neglect (EN) were significant. Table 4 summarizes the results for EA and EN.

Table 6: EA/EN & HbA1C

Models	Variables	Risk compared to unexposed	p-value (95% CI)
Emotional Abuse_1	Model A + depression status + obesity status	Moderate EA: 1.047 Severe EA: 1.082	0.009 (1.011; 1.084) 0.002 (1.028; 1.139)
Emotional Neglect_2	Model A + depression status + obesity status	Moderate EN: 1.053 Severe EN: 1.082	0.009 (1.011; 1.084) 0.002 (1.028; 1.139)

Due to the high association between obesity and T2DM, the obesity status for unexposed and exposed status was analyzed. The obesity risk for those exposed from CM was 1.13 (1.07; 1.18) times greater for those exposed to CM than unexposed. Demographic

covariates and the current depression status were held constant. The current depression status was no longer significant once the CM status was introduced in the model. Table 5 summarizes the results for the obesity outcome.

Table 7: Obesity Outcome & Risk Factor Status

Models	Variables	Risk associated with exposure	p-value (95% CI)
Obesity Status_1	Model A + depression status	1.073	(1.00; 1.14)
Obesity Status_2	Model A + depression + CM	1.13	(1.07; 1.18)

DISCUSSION

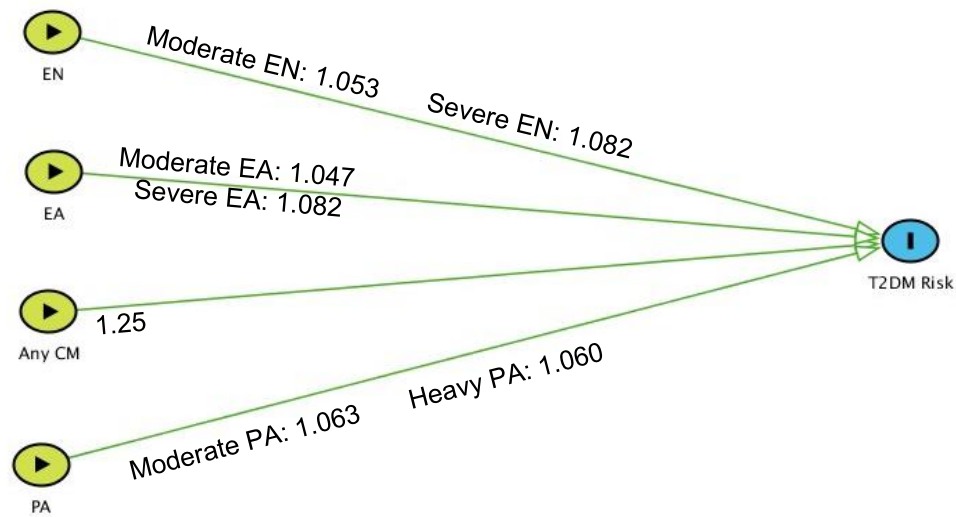
There was no previous literature found on specific types of CM along with severity and its association on T2DM. A meta-study using ACES to determine CM exposure and T2DM risk status found an overall odds ratio of 1.32 (1.16; 1.51). The same study also found an increase in risk for sexual abuse with odds ratio of 1.39 (1.28; 1.52) and overall neglect at odds ratio=1.92 (1.43 to 2.57) (Hao, 2015). A similar study by (Danese, 2008) found a 2.07 times greater risk in hsCRP for participants exposed to CM, but it did not account for obesity status. This study concluded that three types of maltreatment to be significantly associated with an increase risk in T2DM, defined as an HbA1C level of 6.5% or greater. The three types were physical abuse, emotional abuse, and emotional neglect. This association was maintained even when the obesity status and current depression state was added to the model. The relative risk ratio concluded overall exposed versus unexposed was 1.25x (1.21; 1.28). This can be interpreted as participants exposed to any type of CM had a 1.25x risk increase in possessing a HbA1C level of higher than 6.5% compared to those unexposed to any type of CM. This is a significant finding as the obesity status and current depressive state were held constant. Additionally, there was a step-wise increase in risk between unexposed, moderate, and heavy exposure status for both physical abuse, emotional abuse, and emotional neglect. This finding is in agreement with biological plausibility as chronic and severe childhood stress can lead to dysregulation of biological systems. In particular, this dysregulation can result in excess cortisol and hyperglycemia in adulthood (Hornor, 2015). In this same model, sex had the highest value at 1.32 (1.28; 1.35). Females had a 1.32 times greater risk for higher HbA1C than males when CM, obesity, and the

current depressive state was in the model. This was an unexpected finding but does agree with a previous study by (Scherepf, 2014).

As discussed in the introduction section, obesity is a possible confounder for T2DM. It is possible overeating and depression or anxiety is a response to chronic childhood stressors and this can lead to obesity (Scherepf, 2014). There was an increase in risk for obesity 1.13 (1.07; 1.18) for those exposed to CM when the current depressive state was accounted for, further indicating possible long-term effects of exposure to CM.

In summary, the increase in risk for T2DM for participants exposed to any type of CM as compared to unexposed was 1.25 (1.21; 1.28). Different severity and types of CM were analyzed, and three types of CM were significantly associated with HbA1C levels: physical abuse, emotional neglect, and emotional abuse. There was a step-wise increase in risk from moderate to heavy or severe, and these associations were maintained after the obesity status and current depressive state were held constant. Due to recall bias it is possible the odds ratio diminished as the mean age for participants was 54 years old. Participants would have less recall bias towards the overall exposure than specific exposures and severity status. Figure 1 illustrates the study findings.

Figure 1: Overall Study Findings



CONCLUSION

Overall, this study found CM increases the risk of T2DM even when obesity and current depressive state were controlled for in the model. Particularly, moderate to severe physical abuse, emotional abuse, and emotional neglect were significant. Although the results were statistically significant, the odds ratio were small. The purpose of this study was to increase knowledge of the possible long-term effects of different type and severity of CM on T2DM risk. From that perspective, the study met its specific aim as the overall increase in T2DM was higher for those exposed to CM than for individuals without exposure, regardless of current obesity and depressive state. The study findings are in agreement with previous literature and biological plausibility that CM, as a chronic childhood stressor, can result in an increased risk for diabetes mellitus in adulthood.

A retrospective cohort study design was used since exposure status was of primary interest. Due to how the exposure status was collected, through a survey asking participants to recall childhood experiences, recall bias was a possible source of error. The CTQ survey tried to minimize underreporting, but recall bias could remain as it is separate from general recall bias. There could be unintentional lack of memory recall or incorrect memory recall. Ideally, this survey would have taken place at the start of the MIDUS research in 1994. However, CM status was not collected until 2004 at the start of MIDUS 2 Survey Project.

The strength of this study was its ability to control for the two major confounders of T2DM risk: obesity status and depressive state. Also, the study was able to control for participants diagnosed with T2DM in the last 12 months of outcome data collection. In addition, the definition choice for obesity, WHR, has been shown to be a more accurate indicator of T2DM risk factor in this study population. In conclusion, this study met its specific aim to increase knowledge of how CM affects T2DM risks.

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