

Original Article

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Dynamic relationships between depressive symptoms and insulin resistance over 20 years of adulthood

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Abstract

Background. Bidirectional longitudinal relationships between depression and diabetes have been observed, but the dominant direction of their temporal relationships remains controversial.

Methods. The random-intercept cross-lagged panel model decomposes observed variables into a latent intercept representing the traits, and occasion-specific latent ‘state’ variables. This permits correlations to be assessed between the traits, while longitudinal ‘cross-lagged’ associations and cross-sectional correlations can be assessed between occasion-specific latent variables. We examined dynamic relationships between depressive symptoms and insulin resistance across five visits over 20 years of adulthood in the population-based Coronary Artery Risk Development in Young Adults (CARDIA) study. Possible differences based on population group (Black *v.* White participants), sex and years of education were tested. Depressive symptoms and insulin resistance were quantified using the Center for Epidemiologic Studies Depression (CES-D) scale and the homeostatic model assessment for insulin resistance (HOMA-IR), respectively.

Results. Among 4044 participants (baseline mean age 34.9 ± 3.7 years, 53% women, 51% Black participants), HOMA-IR and CES-D traits were weakly correlated ($r = 0.081$, $p = 0.002$). Some occasion-specific correlations, but no cross-lagged associations were observed overall. Longitudinal dynamics of these relationships differed by population groups such that HOMA-IR at age 50 was associated with CES-D score at age 55 ($\beta = 0.076$, $p = 0.038$) in White participants only. Longitudinal dynamics were consistent between sexes and based on education.

Conclusions. The relationship between depressive symptoms and insulin resistance was best characterized by weak correlations between occasion-specific states and enduring traits, with weak evidence that insulin resistance might be temporally associated with subsequent depressive symptoms among White participants later in adulthood.

Introduction

The dominant temporal direction of the association between diabetes and depression remains controversial (Carter & Swardfager, 2016; Darwish, Beroncal, Sison, & Swardfager, 2018; Tabák, Akbaraly, Batty, & Kivimäki, 2014). A meta-analysis reported that depression conferred a prospective diabetes risk ratio of 1.60 over a follow-up period of 3.0–15.6 years, while diabetes conferred a milder risk of depression (pooled risk ratio 1.15) over a follow-up period of 2–12 years (Mezuk, Eaton, Albrecht, & Golden, 2008). These risks were corroborated by pooled odds ratios (OR) of 1.56 *v.* 1.29 in subsequent meta-analyses suggesting that, in terms of magnitude, depression may confer a higher risk for diabetes, compared with the converse (Rotella & Mannucci, 2013a, 2013b).

Using baseline status to predict the status of the other measures over time is not an ideal approach to study the interrelationship between diabetes and depression because the exposures can vary dynamically over time. A cross-lagged panel model (CLPM) has been proposed that includes random intercepts (i.e. the RI-CLPM) to disentangle within-subject associations over

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time from correlations between the two time-invariant traits at the between-subjects level (Hamaker, Kuiper, & Grasman, 2015). Due to the complex time-varying dynamics of depressive symptoms and glycemic measures, it has been difficult to establish the dominance of one risk factor over the other without considering these different sources of information.

No studies have examined the relationship between depressive symptoms and insulin sensitivity prospectively from adulthood to midlife with multiple repeated measurements over time considering their longitudinal dynamics (Knol et al., 2006; Mezuk et al., 2008; Rotella & Mannucci, 2013a, 2013b). Insulin resistance, as quantified from fasting glucose and insulin using the homeostatic model (HOMA-IR), is a defining feature in the development of type 2 diabetes (T2DM) and it has been hypothesized to be part of the pathophysiology of major depressive disorder (de Lyra e Silva et al., 2019). The aim of this study is to determine the longitudinal dynamics between depressive symptoms and insulin resistance over 20 years of adulthood using a RI-CLPM. We hypothesized that depressive symptoms would be associated with insulin resistance, and insulin resistance would be associated with depressive symptoms at subsequent timepoints. In a RI-CLPM, these 'cross-lagged' relationships might offer new insight into the longitudinal dynamics between states of insulin resistance or depression. We further aimed to determine if these dynamics are consistent between the sexes, and between population groups of Blacks and Whites.

Methods

Data source

Data were obtained from the population-based Coronary Artery Risk Development in Young Adults (CARDIA) study, a community-based longitudinal study recruiting participants who had baseline age of 18–30 during 1985–1986 from four sites in the USA (Birmingham, Chicago, Minneapolis, and Oakland) (Friedman et al., 1988). Within 10 years from baseline, participants were followed up every 2–3 years. Afterwards, participants were followed up every 5 years. The study assessed sociodemographic measures, physical and psychological health, and blood measures.

Main study variables

Center for Epidemiologic Studies Depression (CES-D) scale (Radloff, 1977) was used to measure depressive symptoms in the past week with scores ranging from 0 to 60. Higher CES-D scores reflect a higher burden of depressive symptoms. Continuous CES-D scores were used because subthreshold symptoms may be of clinical importance in the context of metabolic disease (Swardfager et al., 2016), and they were linearly related to metabolic parameters (Carter et al., 2016). Insulin resistance was measured by the homeostatic model assessment for insulin resistance (HOMA-IR) (Wallace, Levy, & Matthews, 2004) derived from the product of fasting serum glucose in mg/dl and fasting serum insulin in $\mu\text{U/ml}$ divided by 405. Higher values in HOMA-IR reflect insulin resistance.

Participant selection

Ten years after enrollment into CARDIA, participants were asked to complete the CES-D and blood draws, which were applied concurrently every 5 years thereafter for 20 years (5 timepoints).

Thus, we assessed the dynamics of CES-D scale and HOMA-IR measures for up to 20 years across five visits.

Participants were Black and White, men and women. Those using insulin at the baseline of the analysis, or those diagnosed with cancer, epilepsy, stroke, transient ischemic attack, multiple sclerosis, or thyroid disease, were right censored starting from the visit at which they were diagnosed. Pregnant or breastfeeding women were excluded for the relevant visit. In addition, when a subject had HOMA-IR >20 at a specific visit, data collected from that visit were excluded, as the value was likely from a non-fasting blood sample or a measurement error. The analysis included participants who completed at least one measure of HOMA-IR and CES-D scale at any of these timepoints.

Statistical analysis

The CLPM examines the relationship between one variable at a given timepoint and another variable at the subsequent timepoint (cross-lagged association), controlling for the correlations of each variable on the same variable at the subsequent timepoint (autoregressive associations) and the cross-sectional correlations between the two variables. One drawback of the traditional CLPM is that the within-subjects and between-subjects estimates are conflated, as it does not account for time-invariant trait-like features within each individual (Hamaker et al., 2015). Because there may be trait-like influences (e.g. genetic influences) expected for HOMA-IR and for depressive symptoms, it is necessary to consider stable trait components over time along with autoregressive associations, when longitudinal relationships between variables are investigated (Eid, Holtmann, Santangelo, & Ebner-Priemer, 2017). The RI-CLPM disentangles between-subjects and within-subjects associations by incorporating within-subjects random intercepts as latent trait variables and a between-subjects correlation between trait variables (Hamaker et al., 2015). In addition to a trait-like latent variable, a RI-CLPM also decomposes an observed variable into an occasion-specific latent variable that represents the state. Cross-lagged associations and cross-sectional correlations are assessed among occasion-specific latent variables. The means of the occasion-specific variables were fixed to 0, as they were residual variables.

To test whether autoregressive and cross-lagged associations were constant over time, a constrained model assuming these parameters were constant was compared with the basic model that allowed these parameters to be estimated freely over time, by the Satorra-Bentler scaled χ^2 difference test (Mulder & Hamaker, 2020; Satorra & Bentler, 2010). A p value <0.05 in the χ^2 test indicates that the constrained model is significantly worse than the basic model, providing evidence that the relationships were different at different times.

Previously, sex was shown to modify the association between depression and glucose metabolism (Adriaanse et al., 2008), and Black population was shown to have greater odds of comorbid depression and diabetes (Blazer, Moody-Ayers, Craft-Morgan, & Burchett, 2002). Therefore, a multigroup RI-CLPMs were implemented. The multigroup models were compared with the corresponding nested models that assumed autoregressive and cross-lagged associations were constant between groups, using the Satorra-Bentler scaled χ^2 difference test (Satorra & Bentler, 2010). A p value <0.05 in the χ^2 test indicated that the nested model was significantly worse than the unrestricted multigroup model. The multigroup approach was also used to explore whether people with years of education >12 *v.* ≤ 12 had different longitudinal dynamics.

Because the observed variables were skewed, and data were not complete across all visits, the maximum likelihood robust estimation method with the Huber–White sandwich estimator was used in all analyses. Model fit was assessed using χ^2 test, root mean square error of approximation (RMSEA), standardized root mean square residual (SRMR), and comparative fit index (CFI). A good model fit is denoted by a χ^2 p value <0.05 , RMSEA <0.05 , SRMR <0.05 , and CFI >0.97 (Schermelleh-Engel, Moosbrugger, & Müller, 2003). Analyses were conducted in Mplus 8.3 (Muthén & Muthén, *n.d.*).

Results

Participant characteristics

Of 5115 participants in the CARDIA study, one participant withdrew from the study, 644 participants were excluded from this analysis due to unavailable HOMA-IR or CES-D scale across five timepoints, and 22 participants were further excluded due to baseline insulin use. A total of 3578 data points were censored due to cancer, epilepsy, stroke, transient ischemic attack, multiple sclerosis, or thyroid disease; consequently, 428 participants no longer had available HOMA-IR or CES-D data across five timepoints and were further excluded. There were 210 data points excluded due to pregnancy or breastfeeding, and 46 due to HOMA-IR > 20 ; consequently, 20 participants were further excluded.

A total of 4044 participants were included in the analysis, and a summary of the participant characteristics is shown in Table 1.

Overall associations

The unstratified model with all included participants had a good fit (Table 2). The constrained model with constant cross-lagged and autoregressive associations was significantly worse than the basic model (Table 2; online Supplementary Table S1), indicating that these associations were not consistent over time, favoring the less constrained model (with specific associations that occurred at specific timepoints). Coefficients are summarized in Fig. 1 and in online Supplementary Table S2.

The square of a standardized factor loading for the latent trait variable and the observed variable represents the proportion of variance explained by the trait influence. HOMA-IR showed relatively large factor loadings for the latent trait intercept, and 34.3% (0.586^2) to 64.8% (0.805^2) of the HOMA-IR variance on the observed HOMA-IR quantities were due to trait difference. This indicated that the trait was an important source of stability in HOMA-IR over time. The standardized factor loadings for the intercept decreased over time, indicating that trait differences were becoming less important than states over time.

Autoregressive associations represent carry-over effects of the previous occasion-specific variable on the measurement at the subsequent timepoint. HOMA-IR at the age of 40, 45, and 50 were positively associated with HOMA-IR at its subsequent timepoints ($\alpha = 0.237$, $p < 0.001$; $\alpha = 0.378$, $p < 0.001$; $\alpha = 0.512$, $p < 0.001$) with increasing effect sizes over time. Since the age of 40, HOMA-IR showed an increasing carry-over effect, as the trait became less important over time.

Trait was also an important source of stability in CES-D scale scores over time (48.3–56.5%), but the contribution of the trait to observed CES-D scale scores was relatively consistent across timepoints. Furthermore, CES-D scale scores only at the ages of 35

and 50 were associated (positively) with CES-D scale scores at the subsequent timepoints ($\alpha = 0.122$, $p = 0.002$; $\alpha = 0.161$, $p < 0.001$), indicating weaker carry-over effects.

A weak but significant correlation was observed between the traits of CES-D scale scores and HOMA-IR ($r = 0.081$, $p = 0.002$). No cross-lagged associations were observed between HOMA-IR and CES-D scales at any timepoint. Weak cross-sectional correlations between HOMA-IR and CES-D scales were observed at the ages of 40 and 55 ($r = 0.084$, $p = 0.015$; $r = 0.073$, $p = 0.014$).

Differential relationships by sex, population group, and education

In terms of model fit, the model constraining equal cross-lagged and autoregressive associations between sexes was not significantly worse than its multigroup version where the parameters were freely estimated (Table 2; online Supplementary Table S1). A model constrained to have constant cross-lagged and autoregressive associations between Black and White participants was significantly worse than the multigroup model (Table 2; online Supplementary Table S1). This implies that the interplay between depressive symptoms and insulin resistance differed between Black *v.* White participants, but not between the sexes. Online Supplementary Table S3, and Figs 2 and 3 summarize the estimates from the models grouped by White *v.* Black participants. The model fit indices are summarized in Table 2. In models comparing baseline education >12 *v.* ≤ 12 years, the groups did not show significantly different longitudinal dynamics (Table 2; online Supplementary Table S1). However, there were numeric differences in the trait correlations between men and women as well as between education groups. The two traits were significantly correlated in women ($r = 0.139$, $p < 0.001$) and the group with more advanced years of education ($r = 0.100$, $p = 0.002$), whereas the correlation was not seen in men ($r = 0.038$, $p = 0.333$) or the group with shorter years of education ($r = 0.032$, $p = 0.513$).

In models grouped by Black and White participants, the autoregressive associations of HOMA-IR were greater in White participants ($\alpha = 0.327$, $p = 0.001$; $\alpha = 0.462$, $p < 0.001$; $\alpha = 0.462$, $p < 0.001$; $\alpha = 0.622$, $p < 0.001$) compared with Black participants ($\alpha = 0.200$, $p = 0.010$; $\alpha = 0.311$, $p < 0.001$; $\alpha = 0.425$, $p < 0.001$). The trait contribution of HOMA-IR was stronger for White participants ($\lambda = 0.879$, $p < 0.001$), compared with Black participants ($\lambda = 0.742$, $p < 0.001$) at age 35, but White participants showed a larger reduction in the contribution of the trait over 20 years compared with Black participants.

CES-D scores at the previous time positively were positively associated with CES-D scales score at the age of 40 in Black participants ($\alpha = 0.138$, $p = 0.012$) but not in White participants ($\alpha = 0.065$, $p = 0.244$); however, there were greater autoregressive associations of CES-D scale scores at the age of 55 in White participants ($\alpha = 0.219$, $p < 0.001$) compared with Black participants ($\alpha = 0.123$, $p = 0.026$). In terms of cross-lagged associations, higher HOMA-IR at the age of 50 significantly were significantly associated with higher CES-D scales at the age of 55 ($\beta = 0.076$, $p = 0.038$) in White participants, but not in Black participants ($\beta = 0.002$, $p = 0.962$). Trait influences for CES-D scale were strong in both White participants (λ ranging from 0.702 to 0.742, all $p < 0.001$) and Black participants (λ ranging from 0.673 to 0.746, all $p < 0.001$), with magnitudes that were comparable between these population groups.

Table 1. Participant characteristics

	Overall	Men	Women	Black participants	White participants
Total sample size	4044	1887	2157	2043	2001
Women	2157 (53.3%)	–	–	1139 (55.8%)	1018 (50.9%)
White participants	2001 (49.5%)	983 (52.1%)	1018 (47.2%)	–	–
Baseline education >12 years (<i>n</i> = 3556)	2519 (70.8%)	1129 (68.1%)	1390 (73.2%)	1054 (60.4%)	1465 (80.9%)
Baseline age (<i>n</i> = 3568)	34.92 (3.6)	35.46 (3.43)	34.92 (3.61)	34.37 (3.81)	34.92 (3.70)
CES-D at baseline (<i>n</i> = 3435)	10.54 (8.04)	9.87 (7.31)	11.16 (8.60)	12.02 (8.73)	9.10 (7.01)
CES-D at visit 2 (<i>n</i> = 3105)	9.06 (7.74)	8.47 (6.97)	9.62 (8.36)	10.34 (8.19)	7.89 (7.11)
CES-D at visit 3 (<i>n</i> = 2835)	9.07 (7.52)	8.53 (6.81)	9.57 (8.09)	10.23 (8.05)	8.02 (6.85)
CES-D at visit 4 (<i>n</i> = 2670)	9.31 (7.59)	8.83 (6.92)	9.77 (8.15)	10.16 (8.12)	8.51 (6.96)
CES-D at visit 5 (<i>n</i> = 2323)	8.70 (7.68)	8.45 (7.13)	8.94 (8.17)	9.43 (7.88)	7.98 (7.40)
HOMA-IR at baseline (<i>n</i> = 3412)	2.23 (1.73)	2.29 (1.76)	2.17 (1.69)	2.55 (2.00)	1.92 (1.34)
HOMA-IR at visit 2 (<i>n</i> = 3070)	2.42 (1.93)	2.52 (2.07)	2.32 (1.78)	2.69 (2.10)	2.16 (1.71)
HOMA-IR at visit 3 (<i>n</i> = 2876)	2.63 (2.07)	2.79 (2.27)	2.47 (1.86)	2.96 (2.34)	2.32 (1.73)
HOMA-IR at visit 4 (<i>n</i> = 2661)	2.82 (2.44)	2.99 (2.48)	2.65 (2.38)	3.20 (2.61)	2.45 (2.21)
HOMA-IR at visit 5 (<i>n</i> = 2336)	3.37 (2.89)	3.57 (3.05)	3.18 (2.72)	3.65 (2.96)	3.10 (2.80)
CESD ≥16 at baseline (<i>n</i> = 3435)	728 (21.2%)	284 (17.3%)	444 (24.8%)	467 (27.6%)	261 (15.0%)
CESD ≥16 at visit 2 (<i>n</i> = 3105)	518 (16.7%)	201 (13.4%)	317 (19.7%)	327 (22.0%)	191 (11.8%)
CESD ≥16 at visit 3 (<i>n</i> = 2835)	479 (16.9%)	200 (14.9%)	279 (18.7%)	288 (21.3%)	191 (12.9%)
CESD ≥16 at visit 4 (<i>n</i> = 2670)	445 (16.7%)	178 (13.6%)	267 (19.6%)	265 (20.5%)	180 (13.1%)
CESD ≥16 at visit 5 (<i>n</i> = 2323)	376 (16.2%)	169 (14.8%)	207 (17.5%)	221 (19.3%)	155 (13.2%)
Diagnosed diabetes at baseline (<i>n</i> = 3554)	127 (3.6%)	21 (1.3%)	106 (5.6%)	79 (4.5%)	48 (2.7%)
Diagnosed diabetes at visit 2 (<i>n</i> = 3116)	165 (5.0%)	46 (3.0%)	119 (6.7%)	93 (5.9%)	72 (4.1%)
Diagnosed diabetes at visit 3 (<i>n</i> = 3195)	217 (6.8%)	81 (5.6%)	136 (7.8%)	133 (8.9%)	84 (4.9%)
Diagnosed diabetes at visit 4 (<i>n</i> = 3159)	317 (10.0%)	140 (9.8%)	177 (10.3%)	206 (13.8%)	111 (6.7%)
Diagnosed diabetes at visit 5 (<i>n</i> = 3032)	415 (13.7%)	192 (14.1%)	223 (13.4%)	282 (19.3%)	133 (8.5%)

Mean (s.d.) and count (proportion) were reported for continuous and categorical variables, respectively.

Table 2. Model fit indices

	χ^2	df	<i>p</i> value	RMSEA	90% CI	SRMR	CFI
Overall	136.886	21	<0.001	0.037	0.031, 0.043	0.034	0.976
Multigroup – sex (unconstrained)	156.979	42	<0.001	0.037	0.031, 0.043	0.036	0.977
Multigroup – Black v. White participants (unconstrained)	168.224	42	<0.001	0.039	0.033, 0.045	0.04	0.974
Multigroup – education >12 years v. ≤12 (unconstrained)	103.874	42	<0.001	0.029	0.022, 0.036	0.032	0.983

df, degree of freedom; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual; CFI, comparative fit index.

At the trait level, women showed lower HOMA-IR (standardized difference = -0.149 , $p < 0.001$), but higher CES-D scores than men (standardized difference = 0.162 , $p < 0.001$). Both the traits of HOMA-IR (standardized difference = -0.457 , $p < 0.001$) and CES-D scale (standardized difference = -0.385 , $p < 0.001$) were lower in White participants compared with Black participants. HOMA-IR (standardized difference = 0.448 , $p < 0.001$) but not CES-D scale (standardized difference = -0.091 , $p = 0.056$) was significantly higher in people with >12 years of education. The correlation between the traits was partly attenuated by

adjustment for sex, population group, and baseline education ($r = 0.062$, $p = 0.032$).

Post-hoc analysis

We conducted post-hoc analyses by excluding observations using glucocorticoids, antipsychotics, antidepressants, weight-loss medications, statins, anti-inflammatories, and non-insulin diabetes medications. The results did not change our conclusion that the relationship between depressive symptoms and insulin resistance

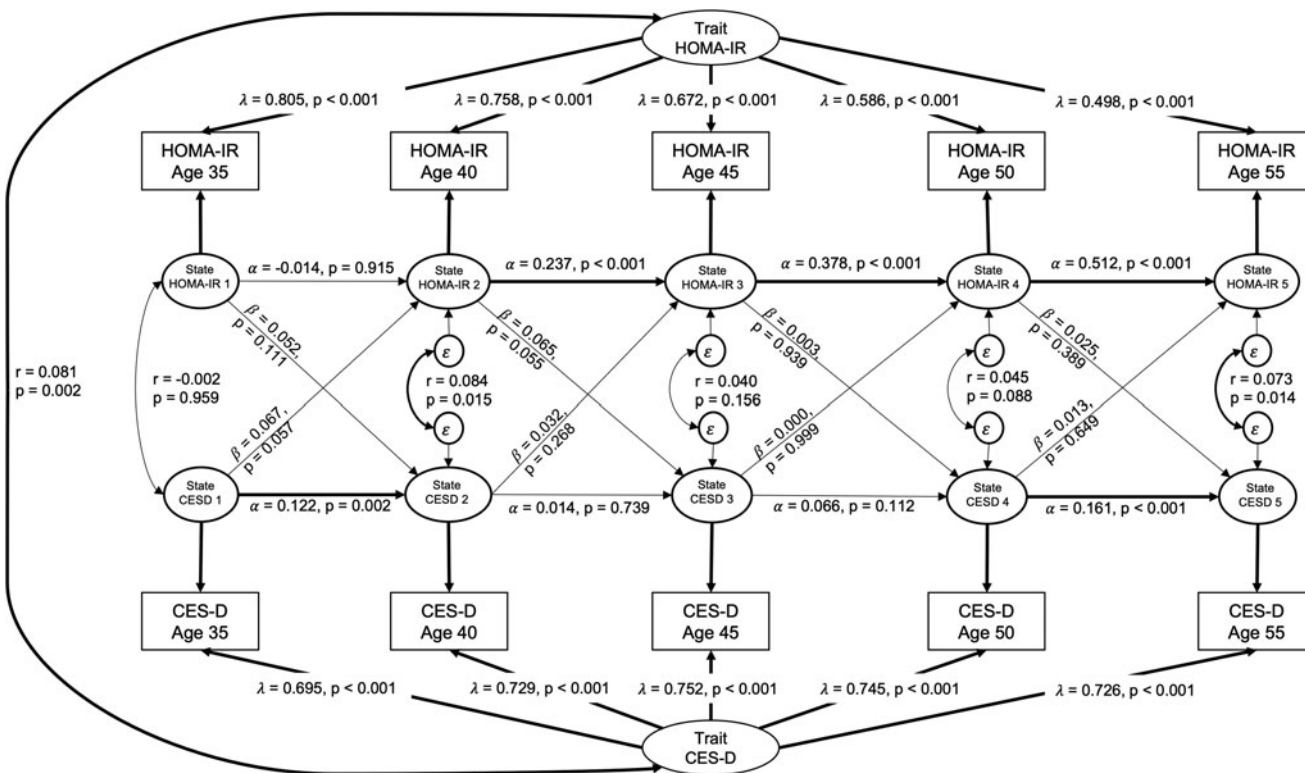


Fig. 1. Graphical representation of the results for the unrestricted model in the unstratified sample. The squares represent observed variables, and the ovals represent latent variables. Correlations are represented by bidirectional arrows, and regression parameters are represented by unidirectional arrows. Arrows in bold indicate significant paths. λ = standardized factor loading; r = correlation coefficient; α = autoregressive standardized regression coefficient; β = cross-lagged standardized regression coefficient, ϵ = occasion-specific residual variable.

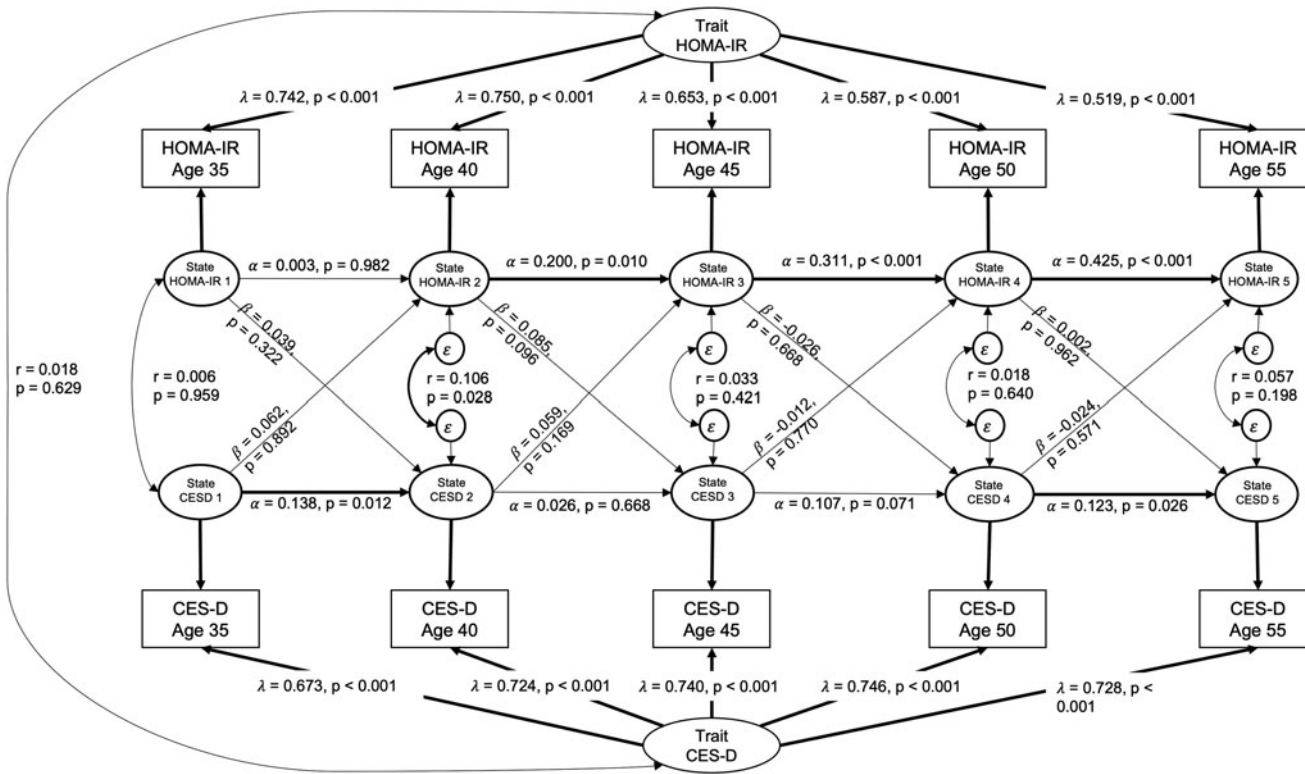


Fig. 2. Graphical representation of the results in the Black population group. The squares represent observed variables, and the ovals represent latent variables. Correlations are represented by bidirectional arrows, and regression parameters are represented by unidirectional arrows. Arrows in bold indicate significant paths. λ = standardized factor loading; r = correlation coefficient; α = autoregressive standardized regression coefficient; β = cross-lagged standardized regression coefficient, ϵ = occasion-specific residual variable.

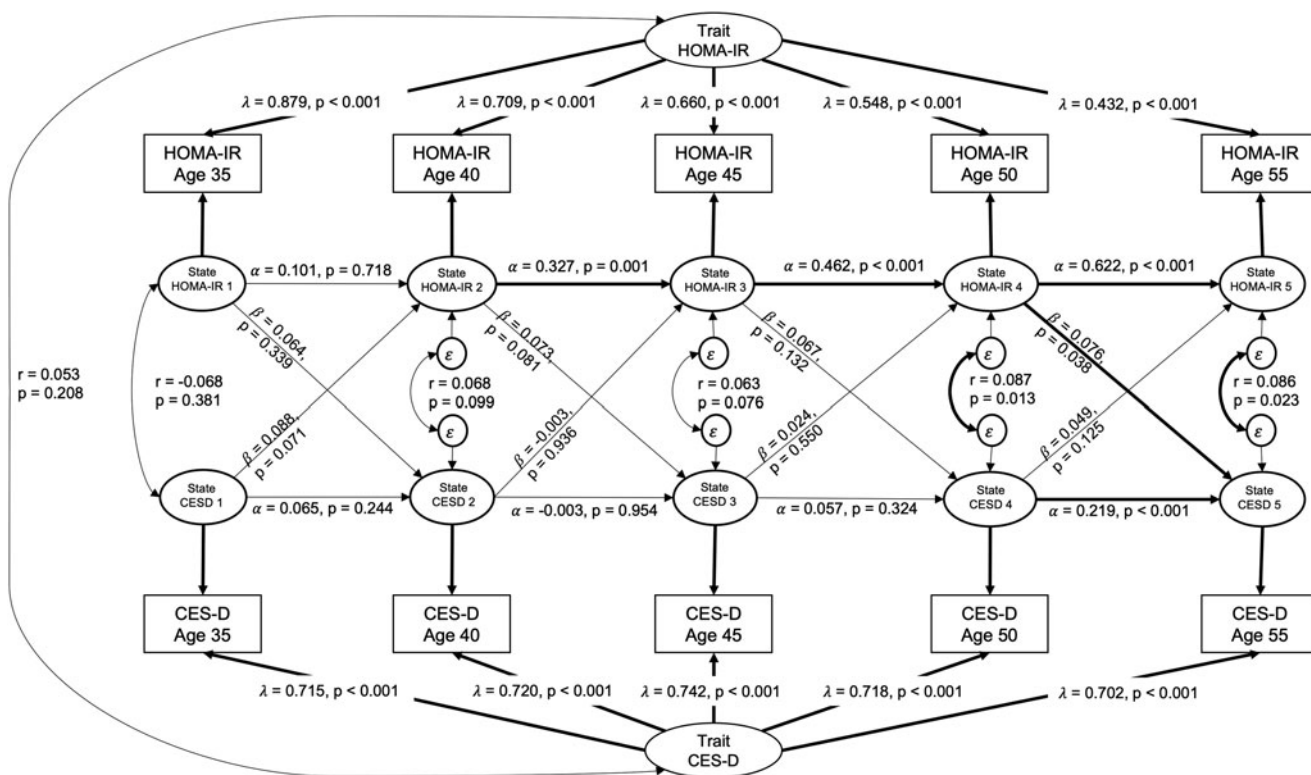


Fig. 3. Graphical representation of the results in the White population group. The squares represent observed variables, and the ovals represent latent variables. Correlations are represented by bidirectional arrows, and regression parameters are represented by unidirectional arrows. Arrows in bold indicate significant paths. λ = standardized factor loading; r = correlation coefficient; α = autoregressive standardized regression coefficient; β = cross-lagged standardized regression coefficient, ϵ = occasion-specific residual variable.

was best characterized by weak correlations between occasion-specific states and enduring traits (online Supplementary Table S4).

Discussion

Important trait influences were found in the overall analysis and in all subgroup analyses. This implies that the traits are important sources of stability in HOMA-IR and depression measurements. The strong trait associations and the adequate fit indices signified that the choice of the RI-CLPM was appropriate. Isolating these trait differences to avoid invalid conclusions about the longitudinal relationships between observed measures, offered a novel viewpoint on the relationship between insulin resistance and depressive symptoms as they fluctuated over a span of 20 years.

A significant but small correlation between the traits of insulin resistance and depressive symptoms was identified from young adulthood to midlife. Additional small correlations between the occasion-specific states were found at the age of 40 and 55, driven by subgroups of Black and White participants, respectively. Autoregressive associations for insulin resistance were identified starting at the age of 40, while autoregressive associations for depressive symptoms were identified sporadically at the ages of 40 and 55, consistent with the phenomena of insulin resistance being progressive, and with dysthymia being at least partially episodic, in nature. It is possible that depressive symptoms reflect, in part, different etiologies at different stages of life (Fiske, Gatz, & Pedersen, 2003), which might be differentially related to insulin sensitivity, particularly since models where associations across time were estimated freely, rather than assumed to be constant,

yielded better fit. In the unstratified model, a lack of evidence for cross-lagged associations was found, which implied that changes in depressive symptoms and insulin resistance had no likely temporal associations on each other of general importance.

The small correlation between depressive symptoms and insulin resistance at the trait level was consistent with a meta-analysis that identified a significant but small correlation between depressive symptoms and insulin resistance (Kan et al., 2013). Three recent cross-sectional studies showed no or small associations between HOMA-IR and depression (Geraets et al., 2020; Lee et al., 2017; Webb et al., 2017). Several cross-sectional studies demonstrated no significant adjusted association between fasting glucose and depressive symptoms in midlife (Aujla et al., 2009; Knol et al., 2007; Mäntyselkä et al., 2011; Mezuk et al., 2013), and one meta-analysis showed no difference in the prevalence of depression between people with and without impaired glucose metabolism (Nouwen et al., 2011). It is important to note that the trait correlation described here is based on enduring dispositions toward depression and insulin resistance, estimated over 20 years of adulthood, whereas the majority of previous studies were based on point measures, which do not disentangle information coming from the trait disposition *v.* from the state at the occasion of measurement. Some additional small correlations between the occasion-specific states were seen, particularly among Black participants at the age of 40 and among White participants at the ages of 50 and 55. These additional occasion-specific state correlations indicate that an individual's state of insulin resistance may be related to their mood state, above and beyond their predisposition to have either trait. Those results provide context for the cross-

sectional association that has been observed between insulin resistance and current but not remitted depressive episodes (Watson *et al.*, 2020), clarifying here that both state and trait relationships exist at the population level. The correlation was also stronger among women and among people with greater education, suggesting previously unidentified heterogeneity.

The present study did not provide evidence to support longitudinal relationships between states of depression and insulin resistance within participants. While we cannot make strong causal inferences from observational data due to the possibility that unmeasured confounders may exist, cross-lagged associations would be most consistent with causal effects, satisfying at least Granger causality criteria (Granger, 1969). Therefore, the lack of these cross-lagged associations provides some evidence for a lack of a causal relationship. In one clinical study of midlife women without diabetes, the reported quantities showed the groups with and without depression had similar HOMA-IR trajectories over time, although an interaction over time was not explicitly tested (Everson-Rose *et al.*, 2004). In an adjusted survival analysis, HOMA-IR was not associated with a higher risk for developing depression (Geraets *et al.*, 2020). The results suggest that prior studies may have been susceptible to overestimating predictive relationships due to the trait correlations (Knol *et al.*, 2006; Mezuk *et al.*, 2008; Rotella & Mannucci, 2013a, 2013b). Conversely, changes in HOMA-IR and depressive symptoms in this community sample, where diabetes was infrequent, might not be meaningful enough to determine the relationships between depression and diabetes *per se*. The majority of participants in the present study were not diagnosed with diabetes or depression; therefore, the results may not generalize to those groups. One study showed that depressive symptom reduction was associated with improved insulin sensitivity in people with depression (Shomaker *et al.*, 2016). Diabetes treatment has been associated with higher depression risk, while untreated diabetes was not (Golden *et al.*, 2008), and antidepressant use may be a risk factor for diabetes (Barnard, Peveler, & Holt, 2013). Bidirectional relationship between depression and insulin resistance might be absent in people without diabetes or depression, necessitating further study in those groups as well as investigation of the impact of medications.

White and Black participants had differential longitudinal associations. White participants showed larger autoregressive associations in CES-D scores at the ages of 40 and 55 than Black participants. Black participants also showed higher CES-D scores at the latent trait level. One US public research study showed that there was a difference in the rate of receiving psychiatric treatment or diagnosis between White and Black participants (Coleman *et al.*, 2016). A Canadian study found an association between mental distress prevalence and ethnic group (Pahwa, Karunanayake, McCrosky, & Thorpe, 2012). In the present study, Black participants also had higher HOMA-IR than White participants at the trait level. This result extends a previous US cross-sectional study showing higher HOMA-IR in Black participants compared with White participants (Raygor *et al.*, 2019), and a meta-analysis showing that Africans had lower insulin sensitivity indices than Caucasians and East Asians (Kodama *et al.*, 2013). In the present study, occasion-specific correlations also differed by population groups, wherein smaller autoregressive associations of HOMA-IR were observed in Black participants; however, it is important to note that smaller autoregressive associations of HOMA-IR do not necessarily indicate less vulnerability to diabetes. The differential autoregressive associations between Black and White participants might be related to cultural, social,

economic, environmental, or biological factors, requiring further investigation. As one possible indicator, educational attainment was not found to significantly affect the longitudinal dynamics of the model.

The hypothesized cross-lagged relationship from depressive symptoms to subsequent insulin resistance was not observed. However, the converse was observed among White participants, wherein a weak cross-lagged association between HOMA-IR at the age of 50 and CES-D scale score at the age of 55 was seen. Its emergence only in later midlife may indicate that the biological relationships between these measures may change with the progression of insulin resistance with aging; however, replication of this finding in further studies in midlife would be required to draw such a conclusion, especially since it was not seen in the whole group, and only in White participants over one interval. The prevalence of diabetes increased over time in this sample, and the extension of these analyses into older ages will be needed to clarify if longitudinal relationships might continue to progress in later life. Notably, a previous study showing longitudinal relationships included older patients (Golden *et al.*, 2008). Of studies included in a meta-analysis exploring the odds of subsequent depression between groups with and without diabetes (Rotella & Mannucci, 2013a, 2013b), many obtained samples from regions where White participants were the majority; however, there seemed to be no clear differences in effect sizes across population groups (Aarts *et al.*, 2009; Bisschop, Kriegsman, Deeg, Beekman, & van Tilburg, 2004; Brown, Majumdar, Newman, & Johnson, 2006; de Jonge *et al.*, 2006; Egberts, Leufkens, Hofman, & Hoes, 1997; Engum, 2007; Golden *et al.*, 2008; Kim *et al.*, 2006; Knol, Geerlings, Grobbee, Egberts, & Heerdink, 2009; Luijendijk, Stricker, Hofman, Wittteman, & Tiemeier, 2008; Maraldi *et al.*, 2007; O'Connor *et al.*, 2009; Palinkas, Lee, & Barrett-Connor, 2004; Pan *et al.*, 2010; Polsky *et al.*, 2005), and those studies did not disentangle state and trait features. The present finding of differential cross-lagged associations between Black and White participants remains to be replicated.

A notable strength of this study is that we utilized a RI-CLPM to study two time-varying variables that may display complex dynamics, rather than a traditional predictive modeling approach considering one factor at baseline as an exposure and the other factor measured later as an outcome. The RI-CLPM, estimating states and traits and then considering autoregressive associations over time, revealed an important autoregressive feature of insulin resistance, whereby a state of insulin resistance contributes to subsequently poorer insulin sensitivity beyond changes in HOMA-IR that progress uniformly with age, and different stabilities of HOMA-IR and CES-D over time (evident in their factor loadings onto their traits). Accounting for these features, the model may offer more reliable estimates for the within-subject associations between HOMA-IR and CES-D over time. The present study may be generalizable to community samples, as the study sample was biracial and covered a wide range of HOMA-IR and CES-D scale scores in both men and women; however, the sample cannot address bidirectional relationships in clinically diagnosed diabetes or depression, as the majority of CARDIA participants had relatively normal HOMA-IR and CES-D scale scores. In addition, there could be links between depressive symptoms and insulin resistance that occur over different timeframes (e.g. cross-lagged associations that occur over days rather than years), and further studies should examine this possibility as data become available; nonetheless, diabetes develops over many years so changes in insulin resistance that occur over this timeframe are clinically

relevant. To retain statistical power and avoid excess model complexity, the current analysis treated CES-D scale scores as a continuous variable and assumed these relationships were linear. Nonetheless, each unit increment in CES-D scale scores may not represent a linear relationship with depressive symptoms or diabetes-related parameters (Golden et al., 2008; Kivimaki et al., 2009). CES-D scores, fasting insulin, and fasting glucose were only measured once at each visit, which may not account for cross-sectional variation or fluctuation in measurement. Lastly, the CARDIA database did not have available HbA1c, and oral glucose tolerance test results across all five timepoints; therefore, their relationships with depressive symptoms were not examined in the current analysis.

Although cross-lagged associations were weak and inconsistent in the current study, factors external to the current analysis might be considered in future studies. The CLPM structure is robust to the impact of time-invariant covariates to some extent; however, it can pose difficulty in adjusting for time-varying covariates that might impact the estimates. Inflammation was associated with the risk for diabetes (Wang et al., 2013), and depression was associated with a higher degree of inflammation (Dowlati et al., 2010). In one mediation analysis (Dona et al., 2020), central adiposity (quantified by waist-to-height ratio) and inflammation (quantified by CRP) were suggested to mediate the relationship between depression and glycemic control (quantified by HbA1c). Inflammatory markers fall reliably with physical activity (Swardfager et al., 2012), which might also be considered as a mediator considering depression and insulin resistance (Rethorst, Bernstein, & Trivedi, 2014). There is an abundant literature on depression and its relationships with body mass index (Luppino et al., 2010), although causality remains to be established (Needham, Epel, Adler, & Kiefe, 2010). The hypothalamic–pituitary–adrenal axis, which regulates stress response, was hypothesized to play a role in the relationship between depression and diabetes (de Lyra e Silva et al., 2019). These and other characteristics might be explored further in still more complex models to further investigate the link between depression and diabetes.

Conclusion

Given the importance of insulin resistance and depressive symptom traits in this community sample, it may be necessary to consider these trait differences to avoid invalid conclusions regarding longitudinal relationships between these characteristics. These traits were weakly correlated with each other, consistent with associations seen in some literature. No compelling bidirectional longitudinal relationships were found in this community sample *in toto*. Longitudinal dynamics differed between Black and White participants, such that insulin resistance was more progressive in White participants, and a temporal association between insulin resistance and subsequent depressive symptoms was seen from age 50 to 55 and only in White participants. Further investigations into the relationships between depressive symptoms and insulin resistance on different timescales and in psychiatric or diabetic populations, as well as what aspects of White and Black population groups studied might modify these relationships, are warranted.

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Conflict of interest. None.

Ethical standards. The population-based Coronary Artery Risk Development in Young Adults (CARDIA) study was reviewed by the research ethic board. The research ethic board at each study site approved the study protocol and procedures. All study participants provided written informed consent to participate in the population-based Coronary Artery Risk Development in Young Adults (CARDIA) study. All study participants provided written informed consent to have their data used for publications. No personally identifiable information is included in the dataset obtained from the population-based Coronary Artery Risk Development in Young Adults (CARDIA) study.

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