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The differential impact of adverse childhood experiences in the development of pre-diabetes in a longitudinal cohort of US adults

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ABSTRACT

Background: ACEs have a dose-response relationship with diabetes. The relationship between ACEs and pre-diabetes is not well known and may represent an effective area for prevention efforts.
Methods: Data from 1054 participants from two waves of the longitudinal MIDUS study were used. Multivariate general linear regression models assessed the relationship between ACEs and biomarker outcomes. Correlation tests and mediation models investigated the relationship between ACE and pre-diabetes.
Results: Individuals reporting ACEs were statistically significantly more likely to have higher BMI (1.13 (0.34–1.92)), higher waist circumference (2.74 (0.72–4.76)), elevated blood fasting insulin levels (2.36 (0.71–4.02)) and higher insulin resistance (HOMA-IR (0.57 (0.08–1.06)). BMI/waist circumference and insulin resistance did not maintain independent relationships with ACEs once HOMA-IR was included in the dichotomized ACE model ($p = 0.05$ and $p = 0.06$, respectively), suggesting the relationship between BMI and ACEs may be mediated by insulin resistance.
Conclusions: These results represent one of the first studies to examine the differential impact of ACEs on a diverse set of clinical pre-diabetes measures. Findings suggest sexual and physical abuse, and financial strain during childhood are important factors associated with higher risk for pre-diabetes, and should be considered during intervention development.

1. Introduction

Adverse childhood experiences (ACEs) represent a broad cascade of events occurring before the age of 18, such as abuse, neglect, and family instability, that produce a state of chronic stress throughout childhood and confer risk for poor health in adulthood.[1–3] Well documented as being predictors of adult morbidity and mortality,[4–8] a single endorsement of an ACE significantly increases risk for diabetes in adulthood, with risk increasing as number of reported ACEs increases.[1,9,10] A growing body of evidence supports the relationship between overall ACEs and diabetes,[9,11,12] the cumulative impact of ACEs and diabetes,[13] and the differential impact of specific ACEs and diabetes.[12,14,15] However, less is known about the mechanisms of influence, and how best to intervene to disrupt the impact of ACEs on developing diabetes.[9] The ACE literature suggests that lifestyle, such as physical activity and nutrition, play an important role in leading to adult morbidity.[16] Specifically, obesity has been suggested as a pathway between ACEs and diabetes.[15] However, this has not been examined in a pre-diabetic population. Additionally, little has been done to provide clinicians with a model for treating patients who have ACEs and are at risk for developing diabetes.[9]

Pre-diabetes is a widely unexplored area in the literature for understanding the impact of ACEs on diabetes and may be an important area of emphasis for intervention in individuals exposed to ACEs.[17] Pre-diabetes is characterized by elevated glucose levels and is consistent with a Hemoglobin A1c (HbA1c) ranging from 5.7–6.4%, fasting plasma glucose (FPG) of 100 mg/dL to 125 mg/dL, or oral glucose tolerance test (OGTT) of 140 mg/dL to 199 mg/dL.[18] Additional risk factors for pre-diabetes include being overweight, being over the age of 45, and family history of diabetes.[19] While designation of pre-diabetes does not necessarily determine a future diagnosis of diabetes, risk increases significantly, and little is known as to whether ACEs serve to compound risk for pre-diabetes, ultimately leading to diabetes. Li and colleagues recently examined whether exposure to ACEs significantly predicts insulin sensitivity and glucose intolerance in a sample of adults and found that among adults endorsing ACEs, greater insulin sensitivity was

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demonstrated among those with ACEs compared to those without as measured by an OGTT, however individual ACE categories were not explored.[17]

As diabetes remains the 7th leading cause of death in the US, representing significant economic burden and hospitalization,[19] two important gaps in the literature warrant greater attention: 1) the biological pathways and the latency period between exposure to ACEs and diabetes development, and 2) the differential impact that individual ACEs have on insulin sensitivity and diabetes related outcomes, i.e. are certain ACEs more detrimental to the development of diabetes compared to others. Addressing these gaps will provide clinicians and researchers with evidence to guide screening and response to ACEs in the healthcare setting. Given the growing focus on trauma informed care,[20] new information is needed to structure screening and treatment for individuals who experiences ACEs. Using a longitudinal cohort of US adults, this study aimed to examine the impact of six ACE categories on the development of pre-diabetes as measured by glycemic control, glucose measures, insulin measures, and obesity markers.

2. Material and methods

2.1. Sample

Data was obtained from the first two waves of the longitudinal study "Midlife in the United States: A National Longitudinal Study of Health and Well-Being" (MIDUS). MIDUS is funded by the National Institute on Aging and is a publicly available dataset. The first phase of dataset was initiated in 1995–1996. The first wave included 7108 participants between the ages of 25 and 74 who completed telephone interviews and self-administered questionnaires (SAQ). Participants were non-institutionalized adults from the contiguous US. Surveys included questions that explored a wide range of demographic characteristics, personality traits and behaviors. Participants from the first wave then participated in a second phase of MIDUS from 2002 to 2004 during which biological and neurological data was collected from 1054 participants. Individuals who accepted the invitation for collection of biologic specimens during the second wave spent 24 h in one of three General Clinical Research Centers, received a physical exam, collection of fasting blood samples, and a urinalysis in the morning after an overnight stay. Biological measures collected as part of the MIDUS wave 2 study included height, weight, waist circumference, waist to hip ratio, blood pressure, hemoglobin A1c, blood fasting glucose levels, and blood fasting insulin levels. Details of recruitment strategy, data collection methods, and detailed sample description have been described elsewhere.[23] MIDUS replaced missing values with respondents mean value. When valid responses were not available responses were recorded as missing and, in some cases, responses were imputed for missing data.[24] The Institutional Review Board provides a waiver to conduct this secondary data analysis using publicly available data.

2.2. Measures

2.2.1. Adverse childhood experiences

The ACE Study Questionnaire[1] was used to identify measures of adverse events experienced during childhood. The MIDUS study collected information on a number of possible ACEs included in the Felitti et al definition of ACE, as well as questions categorized by the MIDUS investigators as additional ACEs surrounding family instability and financial strain. Therefore, a combined set of ACE categories was created to include: emotional abuse, physical abuse, sexual abuse, substance abuse by parents during childhood, family instability, and financial strain.

ACE categories included:

1) Emotional abuse. This item was derived from childhood family background questions in wave 1 and Childhood Trauma Questionnaire (CTQ) completed by participants at the biomarker collection.
2) Physical abuse. This item was derived from childhood family background questions and CTQ, as well questions regarding "ever physically assaulted" before age 18 from wave 2 SAQ.
3) Sexual abuse. This item was also derived CTQ, and question regarding "ever sexually assaulted" before age 18 from wave 2 SAQ.
4) Parental substance abuse. This item referred to substance abuse from a parent during childhood and was derived from childhood background question "what was the main reason father/mother was not working for pay during most of your childhood years? – Alcohol or drug abuse"; additional items assessing this category were derived from the CTQ questions "My parents were too drunk or high to take care of me"; Wave 2 phone interview question "lived with alcoholic during childhood" and "Ever parent drank caused problems" and "Ever parent drugs caused problems".
5) Family instability. This item was measured using the following questions: "Did you live with both of your biological parents up till you were 16?"; "Who was the male head of your household for most of your childhood"; "ever parents divorced" before age 18 at wave 2 SAQ.
6) Financial strain. This item was derived from childhood background questions regarding receipt of welfare; a mother or father having less than a high school education for father; and; report of being 'worse off' than other families.

Each type of ACE was dichotomized. A count of reported ACEs was additionally created for each individual to indicate the number of ACE categories the individual responded positive, as commonly seen in the ACE literature.[1] Finally, a dichotomized ACE variable was created to indicate yes if an individual responded positive to any of the six categories, and no if they responded negative to all six categories.

2.2.2. Biological measures

Biological markers were taken from the second wave of the MIDUS study. The following markers were selected for analysis and categorized based on national recommendations:

1) Body mass index (BMI). BMI was categorized as underweight (<18.5), normal (18.5 to <25), overweight (25.0 to <30), obesity (30.0 or higher), and morbid obesity (40 or higher).[25]
2) Waist circumference in centimeters. Waist circumference was categorized by sex. For men: low (<94), high (94–<102), and very high (102 and greater. For women: low (<80), high (80–<88), and very high 88 and greater).
3) Waist-to-hip ratio. Waist-to-hip ratio was categorized by sex. For men: ideal-very low risk (<0.90), low risk (0.90–0.95), moderate risk (0.95–1.0), and high risk (1.0 and greater). For women: ideal-very low risk (<0.70), low risk (0.70–0.80), moderate risk (0.80–0.85), and high risk (0.85 and greater).
4) Systolic and diastolic blood pressure. Blood pressure was categorized as normal (<120/<80 mm Hg), prehypertension (120–<140/<80 mm Hg), stage 1 hypertension (140–<160 or 90–100 mm Hg), and stage 2 hypertension (≥160 or ≥100 mm Hg).[26]
5) Blood fasting glucose. Blood fasting glucose was categorized as normal (<100), pre-diabetes (100–<126), and diabetes (126+).[27]
6) Blood fasting Insulin. Blood fasting insulin was categorized as normal (<8), low risk (8–<12), moderate risk (12–<25), and high risk (25+).[27]
7) Insulin resistance. Insulin resistance (IR) was categorized as normal (<2), low IR (2–<3), moderate IR (3–<5), and severe IR (5+).[27] Insulin resistance (IR) was determined using the homeostatic model assessment of insulin resistance = HOMA IR calculated as a product of glucose (G0, mg/dL) and insulin (I0, μU/L) divided by the constant 405: HOMAIR = (G0 × I0) / 405. HOMA-IR was a precalculated variable provided in the publicly available dataset. Details of variable calculations can be found through MIDUS ICPSR Codebook.[21,22]

8) Blood hemoglobin A1c. Blood hemoglobin A1c (HbA1c) was categorized as normal (<5.7%), pre-diabetes (5.7%–<6.5%), and diabetes (6.5%+).[27]

2.2.3. Covariates

Covariates include gender (male, female), age group (34–49, 50–64, 65–84). Race was self-reported and categorized as white, black, and other for the purposes of this analysis Educational level was dichotomized as high school diploma or less, higher education, and household income (<25K, 25–<75K, 75K+). Marital status was dichotomized as married and not married (included separated, divorced, widowed, never married, living with someone).

2.3. Statistical analysis

Multivariate general linear regression models were used for each multiple correlated dependent variable to assess the relationship between ACEs and the dependent variables (biomarker outcomes). Each outcome was investigated relative to three ACE definitions: first treating ACE as dichotomous; second as a continuous count of six ACE situations, grouped it into 0, 1, 2, 3, and 4+; and, third treating ACE as 6 separate category variables: emotional abuse, physical abuse, sexual abuse, substance abuse, family instability and financial strain. Univariate and multivariate GLM models were developed to test the unadjusted and adjusted associations for ACEs on each outcome (BMI, waist circumference, waist to hip ratio, systolic blood pressure, diastolic blood pressure, HbA1c, blood fasting glucose levels, blood fasting insulin levels, HOMA-IR insulin resistance). The multivariate tests of the model included ANOVA test for each outcome, MANOVA test for overall effect (all related outcomes as a vector). Finally, we ran a series of correlation tests and mediation models (following steps outlined by Baron and Kenny for mediation)[28] for outcomes found to be significant after fully adjusting for demographics, to investigate the relationship between ACE and these outcomes with other biologic measures taken into account. All analyses were performed using SAS version 9.4 (SAS Institute, Cary NC) with $p < 0.05$ was considered statistically significant.

3. Results

Table 1 displays sample demographics. The cohort for this study was 1054 individuals who completed the initial wave of MIDUS, as well as the biological measures during the second wave. ACE prevalence was high in this cohort with 68.1% endorsing at least one ACE. The majority of the sample was women (54.7%), and most of the population was aged 50–64 (41.3%). This was a very homogenous sample with approximately 93% being White.

Table 1
Sample demographics.

Variables	
Cohort count	1054
Gender	
Male	477 (45.26%)
Female	577 (54.74%)
Age in years at interview	
Mean ± dev (min–max)	55.26 ± 11.78 (34–84)
Median (IQR)	54 (46–64)
Age group	
34–49 yrs	375 (35.58%)
50–64 yrs	435 (41.27%)
65–84 yrs	244 (23.15%)
Race	
White	981 (93.07%)
Black	32 (3.04%)
Other	40 (3.80%)
Education level	
High school diploma or less	254 (24.10%)
Higher education	797 (75.62%)
Marital status	
Married	738 (70.02%)
Household total income	
Mean ± dev (min–max)	76,672 ± 60,409 (0–300,000)
Median (IQR)	62,500 (35,000–101,250)
Household total income category	
<25k	159 (15.09%)
25k–<75k	454 (43.07%)
75k+	419 (39.75%)
Childhood adversity	
With ACE	718 (68.12%)
Childhood adversity count category	
0	336 (31.88%)
1	312 (29.60%)
2	203 (19.26%)
3	104 (9.87%)
4+	99 (9.39%)
Emotional abuse	
With emotional abuse	265 (25.14%)
Physical abuse	
With physical abuse	212 (20.11%)
Sexual abuse	
With sexual abuse	169 (16.03%)
Substance abuse	
With substance abuse	253 (24.00%)
Mental illness	
With mental illness	0 (0.00%)
Family instability	
With family instability	234 (22.20%)
Financial strain	
With financial strain	341 (32.35%)

Table 2 displays unadjusted comparisons of biological markers. Mean BMI with no ACEs was 28.33 ± 5.36 (18.63–45.80), with ACEs the mean BMI had a significant increase to 29.57 ± 6.26 (14.99–60.39) $p = 0.0017$. When examining BMI category by no ACEs versus with ACEs, comparisons were statistically significant, $p = 0.0131$. Specifically, Obesity increased from 28% among those with no ACEs to 35.4% with ACEs. Similarly, waist circumference category Very High was statistically significant, no ACE was 47.16%, with ACE 56.82%; $p = 0.0133$. Mean blood fasting insulin levels (μIU/mL) without ACE was 11.09 ± 8.56 (1–74), with ACE 13.57 ± 13.65 (1–231); $p = 0.0025$. Blood Fasting Insulin Levels category categorized as High Risk (25+) was 6.97% with No ACE, 11.28% with ACE, $p = 0.0051$. Mean HOMA-IR Insulin Resistance without ACE was 2.92 ± 2.94 (0.04–26.93), with ACE 3.52 ± 3.93 (0.18–53.73); $p = 0.0129$.

In the adjusted analysis (Table 3), the presence of an ACE was associated with an increase in BMI ($\beta = 1.13$, 95% CI 0.34–1.92), increase in Waist circumference ($\beta = 2.74$, 95% CI 0.72–4.76), increase in Blood Fasting Insulin ($\beta = 2.36$, 95% CI 0.71–4.02) and increase in HOMA-IR Insulin Resistance ($\beta = 0.57$, 95% CI 0.08–1.06). When including categories of ACEs in the model, physical abuse was associated with an increase in waist circumference ($\beta = 2.78$, 95% CI 0.04–5.52) and increase in blood fasting insulin levels ($\beta = 2.52$, 95% CI 0.25–4.79). Sexual Abuse was associated with an increase in BMI ($\beta = 1.06$, CI 95% 0.00–2.12). Financial Strain was associated with an increase in BMI ($\beta = 0.97$, 95% CI 0.15–1.79), Blood Fasting Glucose levels ($\beta = 3.50$, 95% CI 0.05–6.95), Blood Fasting Insulin levels ($\beta = 2.00$, 95% CI 0.27–3.74) and HOMA-IR Insulin Resistance ($\beta = 0.67$, 95% CI 0.15–1.18).

When investigating ACEs by count per individual, those with one ACE compared to those with none was associated with an increase in BMI of 0.97 (95% CI 0.04–1.90) and increase in Waist circumference of 2.62 (95% CI 0.24–5.00). Reporting two ACEs was associated with an increase in Blood Fasting Insulin levels of 3.56 (95% CI 1.34–5.77) and increase in HOMA-IR Insulin Resistance of 0.73 (95% CI 0.07–1.38), but no significant increase with BMI. Reporting three ACEs was associated with an increase in BMI of 1.87 (95% CI 0.54–3.20) and increase in Waist circumference of 3.67 (95% CI 0.28–7.06). Reporting four or more ACEs was associated with an increase of BMI of 1.88 (95% CI 0.50–3.26), an increase in Waist circumference of 3.86 (95% CI 0.32–7.39), an increase in Blood Fasting Insulin levels of 4.13 (95% CI 1.23–7.04), and an increase in HOMA-IR Insulin Resistance of 1.17 (95% CI 0.31–2.03).

Table 2
Unadjusted comparisons for outcomes by presence of ACE.

	No ACE	With ACE	p-Value
Cohort count	336	718	
Body mass index (exam)			0.0017
Mean ± dev (min–max)	28.33 ± 5.36 (18.63–45.80)	29.57 ± 6.26 (14.99–60.39)	
Median (IQR)	27.21 (24.69–31.47)	28.56 (25.18–32.92)	
BMI category			0.0131
Underweight		4 (0.56%)	
Normal weight	95 (28.36%)	169 (23.54%)	
Overweight	135 (40.30%)	249 (34.68%)	
Obesity	94 (28.06%)	254 (35.38%)	
Morbid obesity	11 (3.28%)	42 (5.85%)	
Waist in centimeters			0.0287
Mean ± dev (min–max)	95.13 ± 15.63 (60.0–187.0)	97.53 ± 16.95 (61.0–266.0)	
Median (IQR)	95.2 (84.0–106.0)	96.5 (86.8–108.0)	
Waist circumference category			0.0133
Low	98 (29.25%)	168 (23.40%)	
High	79 (23.58%)	142 (19.78%)	
Very high	158 (47.16%)	408 (56.82%)	
Waist to hip ratio (exam)			0.6708
Mean ± dev (min–max)	0.89 ± 0.10 (0.66–1.61)	0.89 ± 0.10 (0.62–1.72)	
Median (IQR)	0.89 (0.82–0.97)	0.89 (0.82–0.97)	
WHR category			0.0678
Ideal-very low risk	30 (8.98%)	59 (8.22%)	
Low risk	121 (36.23%)	207 (28.83%)	
Moderate risk	91 (27.25%)	211 (29.39%)	
High risk	92 (27.54%)	241 (33.57%)	
Average of systolic BPs (exam)			0.2817
Mean ± dev (min–max)	130.14 ± 18.20 (85–191)	131.42 ± 17.71 (82–189)	
Median (IQR)	128 (117–141)	130 (119–144)	
Average of diastolic BPs (exam)			0.3242
Mean ± dev (min–max)	74.64 ± 10.19 (49–107)	75.31 ± 10.15 (48–114)	
Median (IQR)	74 (68–82)	75 (68–82)	
Blood pressure			0.2477
Normal blood pressure	97 (28.96%)	177 (24.65%)	
Prehypertension	141 (42.09%)	296 (41.23%)	
Stage 1 hypertension	73 (21.79%)	194 (27.02%)	
Stage 2 hypertension	24 (7.16%)	51 (7.10%)	
Blood fasting insulin levels μIU/mL			0.0025
Mean ± dev (min–max)	11.09 ± 8.56 (1–74)	13.57 ± 13.65 (1–231)	
Median (IQR)	9 (5–14)	10 (6–16)	
Blood fasting insulin levels category			0.0051
Normal (<8)	138 (41.82%)	241 (33.99%)	
Low risk (8–<12)	85 (25.76%)	158 (22.28%)	
Moderate risk (12–<25)	84 (25.45%)	230 (32.44%)	
High risk (25+)	23 (6.97%)	80 (11.28%)	
HOMA-IR: Insulin resistance			0.0129
Mean ± dev (min–max)	2.92 ± 2.94 (0.04–26.93)	3.52 ± 3.93 (0.18–53.73)	
Median (IQR)	2.10 (1.19–3.56)	2.39 (1.42–4.28)	
Insulin resistance category			0.0496
Normal (<2)	156 (47.27%)	288 (40.62%)	
Low IR (2–<3)	72 (21.82%)	150 (21.16%)	
Moderate IR (3–<5)	62 (18.79%)	141 (19.89%)	
Severe IR (5+)	40 (12.12%)	130 (18.34%)	
Blood hemoglobin (HbA1c) (%)			0.9670
Mean ± dev (min–max)	5.99 ± 0.94 (4.70–15.20)	5.99 ± 0.90 (3.80–13.40)	
Median (IQR)	5.80 (5.60–6.15)	5.80 (5.60–6.12)	
Blood hemoglobin (HbA1C) category			0.9472
Normal (<5.7%)	111 (33.33%)	243 (34.37%)	
Prediabetes (5.7%–<6.5%)	179 (53.75%)	374 (52.90%)	
Diabetes (6.5%+)	43 (12.91%)	90 (12.73%)	
Blood fasting glucose levels mg/dL			0.9114
Mean ± dev (min–max)	100.30 ± 24.96 (5–377)	100.48 ± 24.72 (67–418)	
Median (IQR)	96 (90–104)	96 (89–104)	
Blood fasting glucose levels category			0.3497
Normal (<100)	214 (64.85%)	437 (61.64%)	
Prediabetes (100–<126)	92 (27.88%)	228 (32.16%)	
Diabetes (126+)	24 (7.27%)	44 (6.21%)	

In the follow-up analyses to investigate outcomes significantly associated with ACEs after adjustment for demographics, BMI and waist circumference were no longer significant once HOMA-IR was included in the dichotomized ACE model ($p = 0.05$ and $p = 0.06$, respectively). Similar results were seen for ACE count with BMI and waist circumference no longer significantly associated with ACE after inclusion of HOMA-IR ($p = 0.06$ and $p = 0.27$, respectively). While the correlation between BMI and waist circumference was high (0.78) suggesting these outcomes may be similar, the correlation between BMI and HOMA-IR was low (0.38), so loss of significance was not a result of collinearity and instead may suggest mediation.

Table 3
Adjusted analyses for outcomes by three categorization of ACE.

	BMI		WC		W-H Ratio		SBP		DBP		HbA1c		BFG		BFI		HOMA-IR	
	β	CI	β	CI	β	CI	β	CI	β	CI	β	CI	β	CI	β	CI	β	CI
ACE dichotomized																		
ACE	**1.13**	**0.34; 1.92**	**2.74**	**0.72; 4.76**	0.01	−0.00; 0.02	1.19	−1.07; 3.46	0.81	−0.49; 2.11	−0.02	−0.14; 0.10	−0.00	−3.29; 3.28	**2.36**	**0.71; 4.02**	**0.57**	**0.08; 1.06**
ACE count																		
1	**0.97**	**0.04; 1.90**	**2.62**	**0.24; 5.00**	0.01	−0.00; 0.02	1.54	−1.13; 4.21	0.80	−0.73; 2.33	−0.01	−0.15; 0.13	−0.70	−4.58; 3.17	1.61	−0.34; 3.55	0.43	−0.15; 1.00
2	0.68	−0.38; 1.73	1.98	−0.72; 4.67	0.00	−0.01; 0.01	0.04	−2.98; 3.06	1.23	−0.51; 2.96	−0.03	−0.19; 0.13	−0.72	−5.13; 3.68	**3.56**	**−1.34; 5.77**	**0.73**	**0.07; 1.38**
3	**1.87**	**0.54; 3.20**	**3.67**	**0.28; 7.06**	0.01	−0.00; 0.03	2.01	−1.78; 5.81	0.01	−2.17; 2.19	−0.11	−0.31; 0.09	0.66	−4.84; 6.16	0.94	−1.82; 3.71	0.22	−0.60; 1.04
4+	**1.88**	**0.50; 3.26**	**3.86**	**0.32; 7.39**	0.01	−0.01; 0.03	1.61	−2.35; 5.57	0.79	−1.48; 3.07	0.09	−0.12; 0.30	3.48	−2.30; 9.27	**4.13**	**1.23; 7.04**	**1.17**	**0.31; 2.03**
ACE category																		
Emotional abuse	0.12	−0.88; 1.12	−0.41	−2.97; 2.15	−0.00	−0.01; −0.01	0.56	−2.32; 3.44	1.01	−0.64; 2.66	−0.01	−0.16; 0.14	0.34	−3.87; 4.55	−0.67	−2.79; 1.45	−0.14	−0.77; −0.48
Physical abuse	0.87	−0.20; 1.95	**2.78**	**0.04; 5.52**	0.01	−0.01; 0.02	0.34	−2.75; 3.43	−0.84	−2.61; −0.93	0.01	−0.15; 0.18	−1.72	−6.23; 2.79	**2.52**	**0.25; 4.79**	0.42	−0.25; 1.09
Sexual abuse	**1.06**	**0.00; 2.12**	2.33	−0.38; 5.03	0.01	−0.01; 0.02	−0.36	−3.41; 2.68	−0.84	−2.58; −0.91	−0.09	−0.25; 0.07	0.44	−3.99; 4.88	1.31	−0.92; 3.54	0.35	−0.31; 1.01
Substance abuse	0.05	−0.84; 0.93	−1.06	−3.34; 1.22	−0.01	−0.02; −0.01	−0.71	−3.27; 1.86	0.26	−1.21; 1.73	−0.04	−0.17; 0.10	1.70	−2.01; 5.42	−0.14	−2.00; 1.73	0.06	−0.49; 0.61
Family instability	−0.41	−1.32; 0.51	−0.26	−2.60; 2.08	0.00	−0.01; 0.01	1.19	−1.44; 3.83	0.53	−0.98; 2.04	0.01	−0.13; 0.14	−1.27	−5.09; 2.55	0.40	−1.52; 2.32	0.03	−0.54; 0.60
Financial strain	**0.97**	**0.15; 1.79**	1.44	−0.66; 3.55	0.00	−0.01; 0.01	0.34	−2.02; 2.71	0.29	−1.07; 1.64	0.07	−0.05; 0.20	**3.50**	**0.05; 6.95**	**2.00**	**0.27; 3.74**	**0.67**	**0.15; 1.18**

Adjusted coefficients for full models displayed with 95% confidence intervals, bold indicates $p < 0.05$. Adjusted for gender, age, race, educational level, household income, and marital status.
BMI = body mass index; WC = waist circumference; W-H = waist to hip; SBP = systolic blood pressure; DBP = diastolic blood pressure; BFG = blood fasting glucose; BFI = blood fasting insulin.

4. Discussion

Overall, in a longitudinal cohort of US adults, we found that compared to those without ACEs, individuals reporting ACEs were more likely to have higher BMI, higher waist circumference, elevated blood fasting insulin levels, and higher insulin resistance as measured by HOMA-IR. This association was more significant with BMI, waist circumference, and insulin levels than with central/abdominal obesity, blood pressure, or elevated glucose levels. Of interest, BMI/waist circumference and insulin resistance do not maintain independent relationships with ACEs once either factor is accounted for, suggesting the relationship between BMI and ACEs may be mediated by insulin resistance. Finally, among the individual ACE categories, experiences of sexual abuse were associated with higher BMI; experiences of physical abuse was associated with increased fasting insulin as well as waist circumference; and experiences of financial strain was associated with higher BMI, increased fasting glucose, increased fasting insulin, and insulin resistance.

Overall, these results suggest that ACEs increase the risk of pre-diabetes through increased BMI, increased waist circumference, and increased insulin resistance. These results are consistent with existing literature suggesting obesity as an important factor when looking at ACE exposure and adult morbidity.[29–34] Power and colleagues found that in a longitudinal cohort overtime, not only were ACEs associated with increased BMI in adulthood, but specific ACEs differentially accelerated BMI in adulthood compared to individuals who never experienced ACEs.[31] However, the timing of this relationship, and how it influences outcomes over time is unclear. The current results suggest that the association of ACEs with BMI and insulin resistance are not independent of each other, but rather represent important factors within the pathway between ACEs and pre-diabetes in adulthood. In addition to its association with obesity, chronic exposure to psychosocial stressors has been associated with increased corticotropin-releasing factor (CRH) levels, consistent with chronic activation of the HPA axis known to cause elevated cortisol levels and therefore increased insulin resistance.[35,39]

This is the first study to our knowledge to examine the independent relationship that six ACE categories have on pre-diabetes characteristics, including BMI and waist circumference. These results have important clinical, research, and public health implications. Despite the evidence that the literature has provided on the relationship between ACEs and diabetes, little is being done at the clinical level to provide a mechanism for providers to actively screen and tailor treatment plans for adults with a history of ACEs. This may be due in part to the limited training available for students, residents, and clinicians regarding ACE screening at the clinic level.[36] Existing screening procedures have been developed for primary and secondary prevention and take place at the prenatal and pediatric level.[37,38] While some concern has been raised regarding the lack of evidenced based treatments available for ACE screening efforts,[40] as well as the sensitivity surrounding the discussion of ACEs, as it relates directly to pre-diabetes and diabetes, screening would allow providers to better understand patients who may be at increased risk for diagnosis and complications and tailor existing treatment recommendations around risk. Bethell et al recently reviewed methods for ACE assessment and found that population-based surveillance as well as practice-based assessment is an acceptable method for ACE screening.[41] Glowa and colleagues recently pilot tested ACE screening across 3 primary care clinics and found that screening for ACEs in the clinic setting is feasible and sensitivity to questions was not found to be a barrier.[42] Of note, this study found that ACE scores > 4 were more predominate in patients being seen for chronic illness visits. Recognizing that ACE score and exposure may accelerate the diagnosis of pre-diabetes, screening tools would enable providers to tailor treatment plans to suit patients' needs and minimize risk. In addition, recognizing that specific types of ACEs may have a differential effect on outcomes is important for designing and implementing screening. Dube describes the need for ACE screening at the clinic level as a

mechanism for detection that enables informed care, as opposed to diagnosis of traumatic experiences.[43] Utilizing approaches such as detection rather than diagnosis arms clinicians with the proper history and context for developing a health risk profile. This level of comprehensive assessment provides the substrate for tailored treatment plans and informed recommendations for care that may improve health outcomes and lower utilization. This is particularly relevant as the ACE literature provides overwhelming evidence for the dose-response relationship between ACE exposure and diabetes as well as the cost utilization seen among individuals who endorse ACEs compared to those who do not.[38,44] The current study provides new information for clinicians for tertiary prevention by demonstrating the influence of ACEs at the pre-diabetes state and suggests the need to intervene through screening procedures to actively prevent a diagnosis of diabetes.

Additional research is needed to provide evidence for educating clinicians on screening procedures and developing treatment interventions for adults who have experienced ACEs and are at risk for developing pre-diabetes[36] A significant limitation in the diabetes literature exists for whether individuals who have experienced ACEs differ clinically from individuals who have never experienced ACEs, once diabetes manifests. It is unknown if ACEs accelerate the transition from pre-diabetes to diabetes and whether treatment response varies for those who have a history of ACEs compared to those who do not. Understanding these relationships would allow for the development of evidence-based treatment and would guide screening efforts clinically as well as for public health policy and training curriculum. Additionally, the need for caution and sensitivity is highly warranted when it comes to screening for ACEs at any level, however, there remains a lack of evidence for the patients' perspective on conducting ACE screening during the clinical encounter. These results provide the next step for the literature in recognizing that ACE exposure impacts insulin sensitivity and that ACE categories have a differential impact on pre-diabetic characteristics. However, pathways leading to this relationship need to be further elucidated.

5. Limitations

While this study is strengthened by its longitudinal design and large sample size, there are some limitations that should be considered. First, ACEs are self-report and experiences of abuse were not substantiated; however, the literature has shown that recall bias for certain traumatic and significant life experiences are relatively low.[45,46] Second, this sample represented a largely non-Hispanic white population and for this reason may not be generalizable to other more diverse populations. Thirdly, ACEs represent a broad spectrum of experiences that impact individuals across the life course. This study was limited to 6 categories of ACEs and there may be ACEs that relate to pre-diabetes that are not captured in this dataset. Finally, while the individuals in the dataset were followed longitudinally, the biologic measures were collected at one-time point. Therefore, causation between the biologic measures cannot be supported.

6. Conclusion

These results represent one of the first studies to examine the differential impact of ACEs on a diverse set of clinical pre-diabetes measures. These findings suggest that of the ACE categories, sexual abuse, physical abuse, and financial strain during childhood are important factors when considering risk for pre-diabetes, while overall BMI, waist circumference, and insulin resistance should be a focused for intervention development. BMI and insulin resistance are not independent of each other, but rather represent important factors within the pathway between ACEs and pre-diabetes in adulthood. Screening for ACEs during the clinical encounter may improve detection of individuals at risk for developing diabetes. Additional research is needed to examine the pathways underlying this relationship and to further understand if these associations lead to the development of diabetes.

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Authors' contributions

LEE, RJW and JC conceptualized the study. JC was a major contributor in writing and interpreting the manuscript. EG analyzed and interpreted the data in this manuscript. CM and NW were major contributors in writing the manuscript. RW and LE were major contributors in interpreting the data in this manuscript. All authors read and approved the final manuscript.

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