Depression, Inflammation, and the Moderating Role of Metformin:
Results from the Midlife in the United States (MIDUS) Study

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Background

There is a well-established link between depression and aging-related inflammation.

- Numerous studies have shown that depression can spur inflammation and affect physical health, even when controlling for several covariates [1].
- Markers of inflammation are consistently elevated among individuals with major depressive disorder relative to controls [2].

→ Our understanding of moderators of this link remains incomplete.

Previous animal trials have shown compelling evidence that metformin can offset inflammation.

- Metformin, the most widely used drug to treat diabetes, appears to have protective effects for several aging-related mechanisms, including chronic inflammation [3].
- Metformin's anti-inflammatory effects have emerged across various animal models [4].

→ These findings have not yet been extended to human samples.

The current study examines the association between depression and inflammation, specifically the moderating role of metformin usage in middle-aged and older adults.

Research Questions

Hypothesis: Metformin will buffer the association between depression and inflammation, such that those taking metformin will have a weaker association between depression and inflammatory cytokine levels than those *not* taking metformin.

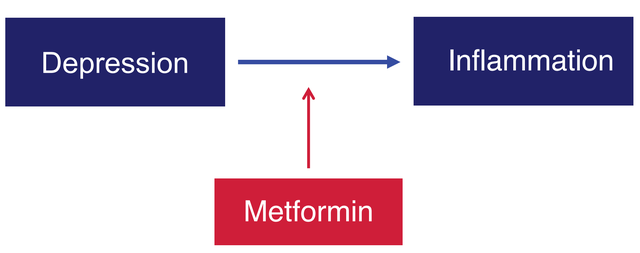


Figure 1. Moderating effect of Metformin on the link between Depression and Inflammation.

Acknowledgements: This work was supported by an award from the National Institute of Aging to Dr. Wilson (NIA R00 AG056667).

Method

Study Sample

1,255 participants in Project 4 of the Midlife in the United States (MIDUS) Study completed measures and provided a blood sample.

Sample Description	M(SD)	Sample Description	N(%)
Age	57.3 (11.5)	**Sex**	713 (56.8%) Female
BMI	29.8 (6.6)	**Race**	978 (77.9%) White

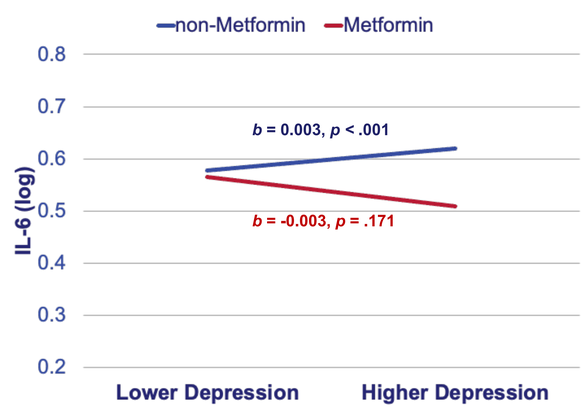
Measures

Depressive Symptoms: Center for Epidemiological Studies-Depression (CES-D) Scale

Inflammatory Markers: Interleukin 6 (IL-6), C-reactive Protein (CRP), Tumor Necrosis Factor alpha (TNF-α)

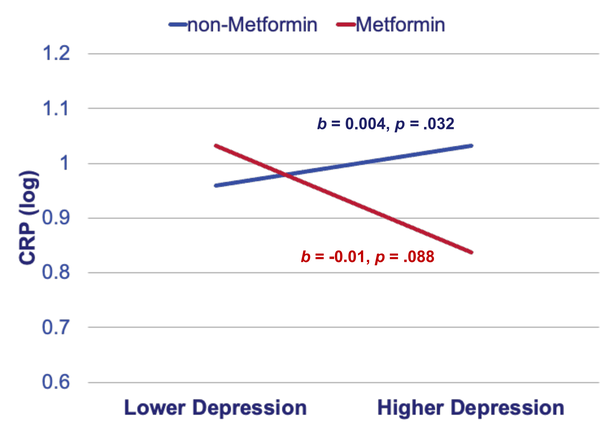
Metformin Usage: Self-report Medication Chart

Results



Higher levels of depressive symptoms were significantly associated with higher IL-6 among those *not* using metformin.

Higher levels of depressive symptoms were significantly associated with higher CRP among those *not* using metformin.



Analyses: Multiple regression models treated log-transformed CRP, IL-6, and TNF alpha as outcomes. Primary covariates included age, sex, BMI, and comorbidity burden. Supplemental covariates included race, education, smoking, exercise, steroid use, and diabetes status. A p-value of less than .05 indicated a significant effect of the predictor variables (depression and metformin use) on our outcome variables.

Results

Table 1. Pearson Correlations between depressive symptoms (measured by the CES-D) and inflammatory markers (CRP, IL-6, and TNF alpha).

	1	2	3	4
1. CES-D	-			
2. CRP	**.12**	-		
3. IL-6	**.11**	**.44**	-	
4. TNF-α	.01	**.23**	**.26**	-

Note. Significant ($p < .05$) bivariate correlations are shown in boldface

Conclusions

Metformin usage may attenuate the relationship between depressive symptoms and inflammatory cytokine levels.

- Higher depression was significantly associated with higher IL-6 and CRP among those *not* using metformin. This effect was not significant among those using metformin.
- Findings support the potential of metformin in mitigating the link between depression, a well-known behavioral risk factor, and inflammation, a key source of biological aging.

Limitations & Future Directions

- This sample includes more white and black participants, and few representing other racial groups. Replication needed in more diverse samples.
- Longitudinal research needed to further examine potential mechanistic relations among depression, metformin, and inflammatory cytokines.

Metformin, an accessible and commonly prescribed anti-diabetic drug, may moderate the link between depression and inflammation.

References

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