Depression, Inflammation, and the Moderating Role of Metformin: Results From the Midlife in the United States Study and Sacramento Area Latino Study on Aging

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Objective: Depression can promote inflammation and accelerate aging. Metformin, a widely prescribed antidiabetic, has shown promising preclinical evidence of aging-related health benefits, including decreased inflammation. The current study examined whether metformin usage buffers the association between depressive symptoms and inflammatory markers in two large samples of middle-aged and older, primarily White adults, and older Latino adults.

Methods: Data from the Midlife in the United States Study (N = 1255) and the Sacramento Area Latino Study on Aging (N = 1786) included information on medication use, depressive symptoms, and inflammatory markers, namely, interleukin 6 (IL-6), tumor necrosis factor α, and C-reactive protein (CRP). These data were merged into a harmonized sample, and the sample group variable was included in a three-way interaction for analysis.

Results: Specifically, in the Midlife in the United States Study sample, metformin buffered the association between depressive symptoms and CRP (b = −0.029, standard error [SE] = 0.013, p = .007) and IL-6 (b = 0.21, SE = 0.010, p = .046), whereas no significant association was found with tumor necrosis factor α. Metformin nonusers displayed higher depressive symptoms associated with elevated CRP (b = 0.01, SE = 0.003, p < .001) and IL-6 (b = 0.011, SE = 0.003, p < .001), whereas this association was not present among metformin users (p values > .068). Conversely, in the Sacramento Area Latino Study on Aging sample, metformin use did not show a significant protective link.

Conclusions: Results from mostly White, highly educated adults supported a mitigating role of metformin in ties between depression, a well-known behavioral risk factor, and inflammation, a key source of biological aging. However, the benefits did not extend to a large sample of older Mexican Americans. The findings reveal a hidden potential benefit of this therapeutic agent and raise important questions around its health equity.

Trial Registration: The study was preregistered on OSF (https://osf.io/c92vw/).

Key words: depression, metformin, inflammation, moderation

Abbreviations:
CES-D = Center for Epidemiologic Studies Depression Scale,
CRP = C-reactive protein, **IL-6** = interleukin-6,
MIDUS = Midlife in the United States Study,
SALSA = Sacramento Area Latino Study on Aging,
SES = socioeconomic status, **TNF-α** = tumor necrosis factor α

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INTRODUCTION

Heightened systemic inflammation is a feature common to many diseases of aging—cardiovascular disease, cancer, diabetes, arthritis, Alzheimer's disease, kidney disease, liver disease, and lung disease. In addition, individuals with elevated circulating inflammation have increased risks of greater frailty over time, faster functional decline, and earlier mortality (1–3). For these reasons, inflammatory markers such as C-reactive protein (CRP), an acute-phase protein, as well as interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α), proinflammatory cytokines, have been identified as among the most promising biomarkers for geroscience research, studies of biological mechanisms promoting aging-related health outcomes, and geroscience-focused clinical trials seeking to slow the biological aging process (4–9).

Depression is a well-established source of chronic inflammation (10–12). A recent meta-analysis of 27 longitudinal studies found a significant, small association between heightened depressive symptoms and subsequent increases in inflammation (13). The authors attributed the small effect magnitude to its wide heterogeneity across individuals and samples, pointing to key moderators such as age. Older adults had stronger associations, suggesting that they may be at greater risk for poor health outcomes related to depression. Therefore, identifying protective factors that may be leveraged in middle and older age is essential. Geroscience is a critical lens that can be used to address these questions (9). Key hallmarks of biological aging, including inflammation, contribute to the overall aging process. Thus, targeting the underlying mechanisms of biological aging, like chronic inflammation, can potentially offset the development or progression of several age-associated chronic illnesses (6,8,14).

Metformin, the first line of therapy for type 2 diabetes, has gained attention in the geroscience field due to growing evidence of its potential anti-aging properties and its ability to reduce inflammation across animal and human patient studies (5,7,15). Indeed, preclinical animal models show metformin's protective effects in several aging hallmarks, including inflammation, which in turn slows the onset and progression of aging-related diseases (16,17). Metformin has shown to delay mortality in animal species like worms and mice (18–21). It also led to decreased cytokine production in bone marrow cells cultured from mice (22) and reduced plasma proinflammatory

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cytokine levels in mice with gestational diabetes (23). In part by reducing inflammation, metformin has shown to lower the risk of myocardial infarction, acute myocarditis, and chronic heart failure in rats (24). Evidence from animal and human epidemiological studies have found that metformin disrupts tumor progression, potentially inducing autophagy of cancer cells by inhibiting inflammatory signaling pathways (18,25).

In human liver and vascular wall cells, metformin has shown to decrease the levels of proinflammatory markers (26,27). A meta-analysis of randomized clinical trials on patients with breast cancer found that metformin reduced CRP levels (28). Data from diabetic patients taking metformin showed that higher dosages were associated with lower circulating proinflammatory cytokine levels (29). Recent studies revealed that metformin use was associated with suppressed production of proinflammatory cytokines in individuals with COVID-19 (30). In a cross-sectional retrospective study of diabetic patients with COVID-19, metformin usage was linked with reduced CRP, IL-6, and TNF-α (31).

Given the growing evidence of metformin's potentially protective effects on inflammation, among other hallmarks of aging, researchers have set out to probe its effects in clinical trials. For example, the Targeting Aging with Metformin study is the first human randomized clinical trial to experimentally test metformin's ability to slow the aging process and prevent the progression of age-related chronic diseases in nondiabetic adults aged 65 to 79 years across 6 years (5). Metformin is approved by the Food and Drug Administration to treat diabetes; however, off-label use has rapidly increased given its pleiotropic benefits beyond glucose control (32). A study documenting metformin prescription rates in the United States from 2000 to 2015 found that by 2015, almost 25% of adults in the United States had a metformin prescription, an 80-fold increase since 2000 (33). Food and Drug Administration–approved metformin prescription rates increased from 2.27 per 1000 individuals to 235. Although this pattern of increase was found across all age and racial/ethnic groups, increases were highly driven by metformin use among middle-aged to older adults, female individuals, and Hispanic individuals. Metformin use has demonstrated efficacy in glycemic control, as reflected by A1C levels, particularly in minority populations, specifically African American individuals compared with European American individuals (34). A few comprehensive systematic reviews reference studies highlighting metformin's effectiveness in inflammation reduction (34–36). However, these studies frequently omit racial and ethnic demographic breakdowns of participant samples. Although the link between metformin and inflammation reduction has been established in studies with large samples, the racial/ethnic composition is often underreported and likely overrepresents White non-Hispanic individuals.

Moreover, in cases where such details are provided, a predominant majority of the samples comprise White non-Hispanic individuals, and a smaller subset of studies indicate a representation of approximately 9.1% to 10.6% for Hispanic individuals (37,38). The widespread use of metformin highlights the significance of comprehending its broader consequences, particularly considering the well-documented association between metformin use and lower levels of inflammation, necessitating further investigation into its anti-inflammatory effects in diverse populations and settings.

Because depression and chronic inflammation compound the risk for poor outcomes in middle and older age, it is critical to understand the role that moderators have in mitigating this link (39,40). Metformin may contribute to the heterogeneity in the ties between depression and inflammation by weakening the association. In other words, this antidiabetic drug, widely used for a variety of off-label purposes and suspected of having antiaging effects, may also inadvertently protect middle-aged and older adults from the inflammatory risks of heightened depressive symptoms.

In the present study, we examined associations among depressive symptoms, metformin use, and inflammatory outcomes (CRP, IL-6, and TNF-α) in a harmonized sample of two middle-aged and older adult samples—participants from the Midlife in the United States Study (MIDUS) and the Sacramento Area Latino Study on Aging (SALSA). The use of two large samples, including one that consists of minoritized individuals, is a key feature of this study. Indeed, studies of health and aging tend to overrepresent White, highly educated individuals, with fewer individuals of color and from disadvantaged backgrounds. Expanding the investigation to incorporate greater diversity is crucial, especially in the field of geroscience, where a critical aim is to uncover sources of variance from social factors that contribute to processes of healthy aging (41). Moreover, testing hypotheses in two distinct samples enhances the robustness and replicability of the empirical patterns across diverse populations. Given the compelling evidence of its anti-inflammatory properties, we hypothesized that metformin would buffer the link between depressive symptoms and inflammatory markers—in particular, CRP and IL-6—across both samples. Unlike CRP and IL-6, TNF-α did not share a significant association with prior depression in a recent meta-analysis (13). Thus, associations with TNF-α were considered exploratory.

Aging plays a central role in the associations among depression, metformin use, and markers of inflammation within our study samples. Inflammation increases with age, leading to the phenomenon known as inflammaging (42). This is driven by an imbalance between proinflammatory and anti-inflammatory mechanisms (43). This heightened inflammation that comes with advancing age contributes to age-related diseases and cellular-level aging (44). In tandem, the prevalence of type 2 diabetes notably rises with advancing age, resulting in a corresponding tendency for adults on metformin to be older (45,46). In addition, depression is prevalent among older individuals, with a pooled estimate of 31.7% in the global population (47). Although high rates of depression are not exclusive to this age group, its consequences cannot be disregarded. Indeed, it often goes untreated or unnoticed in older adults, especially among minority groups (48–50). Consequently, we further investigate the role of age in the associations among depressive symptoms, metformin use, and inflammatory outcomes in the harmonized sample of MIDUS and SALSA. Based on previous research and the rationale of the current study, we hypothesize that age may modulate the associations among depressive symptoms, metformin use, and inflammatory outcomes. We expected that older age would be associated with higher inflammation. We assessed whether the moderating effect of metformin varied based on age. Our approach was exploratory, as the literature was not clear on whether this

buffering effect would be stronger or weaker among older adults.

METHODS

Participants

The current study used data from participants in both the MIDUS and SALSA studies. Data collection of a national sample (ages 25–74 years) for the first wave of MIDUS (MIDUS I) was conducted in 1995 to 1996 (51). Participants were given a self-administered questionnaire, and those who filled it out were invited to complete a telephone interview. A follow-up study, the MIDUS Biomarker Project, was conducted in 2005 to 2006, as part of the second wave of data collection (MIDUS II) (52). The Biomarker Project included a subsample of the original participants and aimed to investigate the biopsychosocial factors that contribute to health outcomes. Data for the current analyses were from the baseline data of 1255 participants from the Biomarker Project. Participants traveled to one of three General Clinical Research Centers in the United States (University of California–Los Angeles, University of Wisconsin, and Georgetown University) and provided blood samples for biomarker assays. The MIDUS Biomarker Project protocol has been previously described in further detail (52,53).

SALSA is a longitudinal study of cognition, health, and aging in a cohort of community-dwelling Mexican American adults aged 60 to 101 years in the Sacramento area. Participants completed medical examinations and provided biological and survey data to investigate a wide array of cognitive, physical, and social factors that may affect health and aging outcomes. Data for the current analyses were drawn from SALSA baseline data (N = 1786) collected at the time of enrollment (1998–1999). Details of the study protocol have been previously described (54). Both studies were reviewed and approved by institutional review boards at the participating institutions (MIDUS: University of Wisconsin–Madison; SALSA: University of California–Davis, University of California–San Francisco). Both MIDUS II (https://www.icpsr.umich.edu/web/NACDA/studies/4652) and SALSA study data are publicly available (https://www.icpsr.umich.edu/web/NACDA/series/247).

Measures

Sample Group

All study variables were retrieved from the SALSA and MIDUS datasets and were harmonized into a single dataset. Sample membership was included as a categorical variable in the analysis to examine potential differences between two distinct samples, MIDUS and SALSA. Sample group was coded into a value of 0 indicating MIDUS participants and a value of 1 indicating SALSA participants.

Depressive Symptoms

Depressive symptoms were measured in both MIDUS and SALSA using the Center for Epidemiologic Studies Depression Scale (CES-D), which has been widely used and validated in older adults (55–57). Participants were instructed to answer items (e.g., "I felt downhearted and blue") with reference to the past week, and responses were rated on a four-point scale from *rarely or none of the time* (0) to *most or all of the time* (3). CES-D total scores can range from 0 to 60, with higher scores indicating greater depressive symptoms. Cronbach's α for the CES-D was .88 in the MIDUS Biomarker sample and .90 in the SALSA sample.

Inflammatory Markers

Inflammation levels were assessed via immunoassays of three markers of inflammation: CRP, IL-6, and TNF-α. MIDUS assay procedures have been previously detailed (53). Briefly, participants of the MIDUS Biomarker Project provided fasting blood samples on the second day of their in-person visit at one of three General Clinical Research Centers. Frozen samples were shipped to the MIDUS Biocore Laboratory for analysis (University of Wisconsin, Madison, Wisconsin). Serum CRP levels were measured with a BN II nephelometer (Siemens/Dade Behring Inc., Deerfield, Illinois) using a particle-enhanced immunonephelometric assay. Samples that fell below the CRP detection threshold were rerun by immunoelectrochemiluminescence via a high-sensitivity assay kit (Meso Scale Diagnostics, No. K151STG). The interassay coefficient of variation (CV) was 5.16%, and the intra-assay CV was 4.1%. Blood serum IL-6 and TNF-α levels were measured using a V-plex Custom Human Cytokine Kit (Meso Scale Diagnostics, No. K151A0H-2). The interassay CV was 15%, and the intra-assay CV was 4.73% for IL-6. For TNF-α, the interassay CV was 7%, and the intra-assay CV was 3.19%. Intra-assay and interassay CVs for these samples were within an established acceptable range (<20%) (58).

Details of the SALSA assay method have been previously described (59). In short, participants provided baseline fasting blood samples. Serum samples were stored at −70°C at the Medical Center Clinical Laboratory at the University of California, Davis. High-sensitivity CRP was measured using the CRP Ultra-Wide Range Reagent Kit latex-enhanced immunoassay (Equal Diagnostics, Exton, Pennsylvania). IL-6 and TNF-α levels were measured using the QuantiGlo Chemiluminescent Immunoassay (R&D Systems, Minneapolis, Minnesota).

Metformin Use

Use of metformin, a commonly prescribed antidiabetic drug, was determined in both MIDUS and SALSA using medication usage data collected at baseline and recoded as a binary variable to be assessed as a moderator in the current analyses. MIDUS participants were instructed to bring all medications in original bottles to their in-person biomarker visit to record accurate medication names and dosages (53). During baseline interviews, SALSA participants provided their medications (prescription and OTC) for medication data collection (59). Combination drugs containing metformin and another drug—for example, Actoplus Met (metformin and pioglitazone), Avandamet (metformin and rosiglitazone)—were included among the metformin users.

Covariates

Age, sex, body mass index (BMI; calculated from measured height and weight), and comorbidities were included as key covariates in the primary analyses. Minority status,

smoking, exercise, steroid use, and diabetes status were included as covariates in supplementary analyses. Comorbidities were calculated for both samples using a modified Charlson Comorbidity Index based on self-report of having chronic health conditions (1 = yes, 0 = no) (60,61). In MIDUS and SALSA, participants were asked about current or past chronic health conditions related to heart problems, transient ischemic attack or stroke, liver problems, and cancer (excluding minor skin cancer). Each chronic health condition was given a point and then summed to calculate a comorbidity burden score for each participant. For both MIDUS and SALSA, the steroid use variable was binary coded (1 = yes, 0 = no) if a steroid drug (e.g., prednisone, cortisone, or methylprednisone) was listed in medication usage data. Minority status in MIDUS was coded as a binary variable (1 = non-Hispanic White, 0 = other races/ethnicities). Of note, minority status was a constant in SALSA, as the full sample is of Hispanic/Latino ethnicity. Diabetes status was based on a binary coded variable (1 = diabetic, 0 = not diabetic) based on fasting salivary glucose of ≥126 mg/dl (62). Smoking status in both samples was coded dichotomously (1 = current or former smoker, 0 = never smoker).

Analytic Plan

Data from the MIDUS and SALSA samples were harmonized into a single dataset across parallel study variables. A sample group variable was computed to indicate sample group membership (1 = SALSA; 0 = MIDUS). We hypothesized that metformin would buffer the association between depressive symptoms and inflammatory markers. To test this, we regressed the three inflammatory markers (CRP, IL-6, and TNF-α) onto depressive symptoms (centered at the sample average), metformin use (coded as a binary variable), sample group membership (coded as a binary variable), and their three-way interaction. By including this three-way interaction, we can explore whether the impact of depressive symptoms on inflammatory markers differs based on whether individuals are using metformin and which sample group they belong to. Regression analyses were performed in SPSS version 29. Models covaried for age, sex, BMI, and comorbidities. Participants with missing data on specific inflammatory markers were excluded from the respective regression analyses. High CRP values exceeding greater than 20.0 mg/L were excluded because of potential acute factors (e.g., injury or active infection) (63–65). To address skewness, *z*-scored CRP, IL-6, and TNF-α were log-transformed. Residuals of the log-transformed inflammatory markers were examined, and outliers (>3 standard deviations) were excluded for IL-6 in both MIDUS (2 cases) and SALSA (22 cases) samples. For models with statistically significant interactions ($p < .05$), simple slopes were probed. In models with nonsignificant interactions, the interaction term was removed to explore whether the expected two-way interactions or main effects were present. Furthermore, supplemental analyses were performed to test the robustness of results to additional health-related and demographic covariates: smoking, exercise, steroid use, diabetes status, and minority status. Given its relevance, supplemental analyses probing the role of age in these associations were also performed. To test this, we regressed inflammatory markers onto depressive symptoms, metformin use, sample group membership, age, and their four-way interaction. Nonsignificant interactions were trimmed to explore lower-order effects.

RESULTS

Table 1 shows descriptive statistics for MIDUS and SALSA study samples. Most notable differences between samples included age, minority status, education, and comorbidity burden. MIDUS participants' average age was 57.32 years (SD = 11.55 years; range, 35–86 years). The average age of SALSA participants was 70.64 (SD = 7.11 years, range, 60–101 years). A majority of MIDUS participants were White (78.2%), whereas the SALSA sample consisted entirely of Mexican American participants. Regarding comorbidity burden, approximately one-third of the MIDUS sample (35.7%) reported one or more comorbidities, compared with 52.6% in the SALSA sample. The proportions of diabetic metformin users were similar across MIDUS (prediabetic, 24.4%; diabetic, 74.4%) and SALSA (prediabetic, 21.5%; diabetic, 67.7%). MIDUS and SALSA participants were highly similar in their average BMIs (MIDUS, 29.77 [SD = 6.63]; SALSA, 29.68 [SD = 5.91]) and proportions of participants using metformin (MIDUS, 7.2% [$n = 90$]; SALSA, 7.4% [$n = 133$]). In MIDUS, 15% of participants were diabetic, whereas 23.5% were diabetic in SALSA. More than half (52.1%) of MIDUS participants were prediabetic compared with approximately one-quarter (24.5%) of the sample in SALSA.

Table 1 displays the results of *t* tests and χ^2 tests, revealing significant differences between the SALSA and MIDUS samples. SALSA participants were significantly older and had higher depression scores, a greater comorbidity burden, a higher prevalence of diabetes, and a higher prevalence of smoking compared with MIDUS participants. In addition, SALSA individuals demonstrated significantly higher levels across all inflammatory markers in comparison to MIDUS participants. Bivariate correlations among main study variables across both samples are shown in Table 2. As expected, in both MIDUS and SALSA samples, depressive symptoms (CES-D) and all three inflammatory markers were positively correlated, with one exception of TNF-α in MIDUS.

C-reactive protein

Results showed that the three-way interaction between depressive symptoms, metformin use, and sample group significantly predicted log-transformed CRP ($b = 0.036$, standard error [SE] = 0.013, $p = .005$, 95% CI = 0.011–0.061, $f^2 = 0.21$). Thus, the interaction between metformin use and depressive symptoms varies based on sample group membership. Sample group significantly moderated the association between depressive symptoms and CRP among people not taking metformin ($b = 0.008$, SE = 0.004, $p = .037$, 95% CI = 0.000–0.015) and those taking metformin ($b = 0.028$, SE = 0.012, $p = .020$, 95% CI = 0.004–0.052) in both SALSA and MIDUS. Simple slopes were probed to uncover patterns.

MIDUS

Metformin significantly moderated the association between depressive symptoms and log-transformed CRP among those in MIDUS ($b = -0.029$, SE = 0.011, $p = .007$, 95% CI = −0.051 to −0.008). That is, among MIDUS individuals not

TABLE 1. Descriptive Statistics for MIDUS and SALSA

Variables	MIDUS, Mean ± SD (Range) or %	SALSA, Mean ± SD (Range) or %	t or χ^2
Age, y	57.36 ± 11.56 (35–86)	70.64 ± 7.11 (59–101)	$t = -36.00$*
Sex	56.5% F	58.3% F	$\chi^2 = 1.02$
Minority status	21.2%	100%	—
BMI, kg/m^2	29.69 ± 6.55 (14.99–65.09)	29.68 ± 5.91 (15.51–82.72)	$t = 0.013$
Comorbidity burden	0.18 ± 0.43 (0–2)	0.27 ± 0.50 (0–3)	$t = -5.40$*
Metformin users	7.2%	7.4%	$\chi^2 = 0.036$
Diabetes	8.5%	23.4%	$\chi^2 = 110.91$*
CES-D scores	8.72 ± 8.21 (0–54)	10.02 ± 10.62 (0–54)	$t = -3.74$*
Smoking	47.6%	53.9%	$\chi^2 = 1506.39$*
Steroid use	0.9%	1.1%	$\chi^2 = 0.223$
Inflammatory markers			
CRP, pg/ml	2.59 ± 3.01 (0.02–19.60)	4.50 ± 4.25 (0.10–19.90)	$t = -13.68$*
IL-6, pg/ml	1.00 ± 0.70 (0.11–5.08)	4.67 ± 3.38 (0.54–23.64)	$t = -41.35$*
TNF-α, pg/ml	2.14 ± 0.67 (0.31–5.06)	4.09 ± 1.74 (1.10–12.76)	$t = -39.44$*

MIDUS = Midlife in the United States Study; SALSA = Sacramento Area Latino Study on Aging; SD = standard deviation; BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression Scale; CRP = C-reactive protein; IL-6 = interleukin 6; TNF-α = tumor necrosis factor α.

Sex = percentage of participants who are female. Minority status = percentage of participants of minority status. Comorbidity burden was indicated by the count of self-reported experience of comorbidities including heart problems, stroke, cancer, and/or liver problems. Diabetes = percentage of participants who are diabetic based on fasting glucose levels. Smoking = current or former smoker. Independent-samples t tests (df range, 1695–2935) were conducted for continuous variables, whereas χ^2 tests of independence (df range, 1–2) were used for categorical variables. No statistical test was conducted for minority status because it was a constant variable in one sample (SALSA).

* $p < .001$.

taking metformin, higher depressive symptoms were associated with higher CRP ($b = 0.01$, SE = 0.003, $p < .001$, 95% CI = 0.004–0.016). Conversely, the link was not significant among MIDUS metformin users ($b = -0.019$, SE = 0.011, $p = .068$, 95% CI = −0.040 to 0.001). Simple slopes are depicted in Figure 1A.

SALSA

Metformin did not moderate the link between depressive symptoms and log-transformed CRP among those in SALSA ($p = .304$, 95% CI = −0.006 to 0.019). The main effect of depressive symptoms on CRP was also not significant ($p = .136$, 95% CI = −0.003 to 0.021), as was the main effect of metformin use on CRP ($p = .429$, 95% CI = −0.094 to 0.221).

Interleukin 6

Results showed that the three-way interaction between depressive symptoms, metformin use, and sample group predicted log-transformed IL-6 ($b = 0.024$, SE = 0.012, $p = .044$, 95% CI = 0.001–0.048, $f^2 = 0.17$). Thus, the interaction between metformin use and depressive symptoms varies based on sample group membership. However, sample group did not moderate the association between depressive symptoms and IL-6 among people taking metformin ($p = .132$, 95% CI =

TABLE 2. Correlations Among Primary Study Variables in MIDUS and SALSA

	1	2	3	4	5	6	7
1. CES-D	—	0.10**	0.09**	0.06**	0.03	0.02	0.11**
2. CRP	0.14**	—	0.40**	0.14**	−0.04	0.26**	0.04`
3. IL-6	0.10**	0.41**	—	0.30**	0.14**	0.10**	0.08**
4. TNF-α	0.002	0.16**	0.26**	—	0.17**	0.03	0.08**
5. Age	−0.16**	0.15**	0.15**	0.26**	—	−0.14**	0.06**
6. BMI	0.11**	0.30**	0.30**	0.16**	−0.05	—	−0.02
7. Comorbidities	0.09**	0.18**	0.18**	0.20**	0.31**	0.02	—

MIDUS = Midlife in the United States Study; SALSA = Sacramento Area Latino Study on Aging; CES-D = Center for Epidemiologic Studies Depression Scale; CRP = C-reactive protein (log); IL-6 = interleukin 6 (log); TNF-α = tumor necrosis factor α (log); BMI = body mass index.

Only continuous variables are included. Correlations for MIDUS are below the diagonal and correlations for SALSA are above the diagonal.

* $p < .05$.

** $p < .01$.

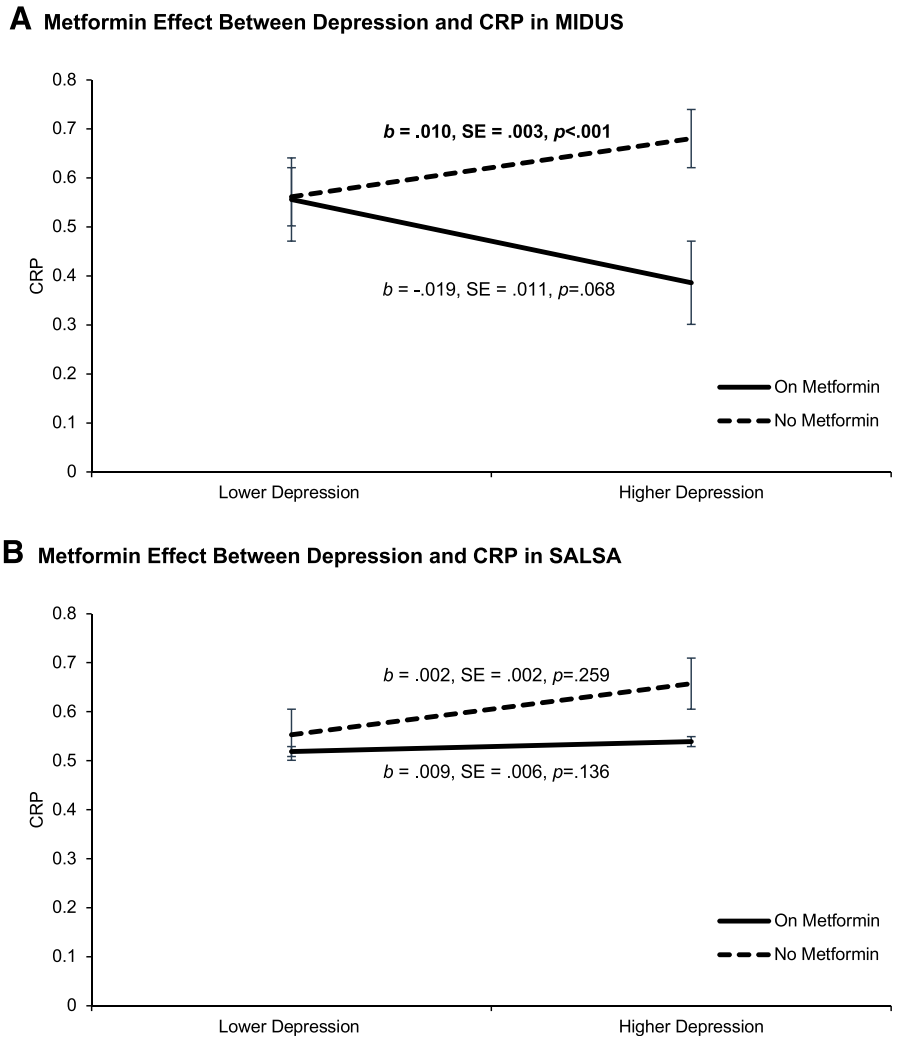

FIGURE 1. Associations of depressive symptoms with inflammatory marker CRP at different levels of metformin use in the MIDUS and SALSA samples. Parameter estimates (*b*) are provided for each slope. Estimates in boldface are significant ($p < .05$). CRP = C-reactive protein; MIDUS = Midlife in the United States Study; SALSA = Sacramento Area Latino Study on Aging; SE = standard error.

−0.005 to 0.040) and those not taking metformin ($p = .051$, 95% CI = −0.014 to 0.000) in both SALSA and MIDUS. Simple slopes were probed to uncover patterns.

MIDUS

Metformin significantly moderated the association between depressive symptoms and log-transformed IL-6 among those in MIDUS ($b = 0.21$, SE = 0.010, $p = .046$, 95% CI = 0.000–0.041). Simple slope analyses revealed the same trend: among MIDUS individuals not taking metformin, higher depressive symptoms were associated with higher IL-6 ($b = 0.011$, SE = 0.003, $p < .001$, 95% CI = 0.005–0.017). Conversely, the link was not significant among MIDUS metformin users ($b = -0.010$, SE = 0.010, $p = .329$, 95% CI = −0.029 to 0.010). Simple slopes are depicted in Figure 2A.

SALSA

Metformin did not moderate the link between depressive symptoms and log-transformed IL-6 among those in SALSA ($p = .557$, 95% CI = −0.016 to 0.008). The main effect of depressive symptoms on IL-6 was also not significant ($p = .188$, 95% CI = −0.004 to 0.019), as was the main effect of metformin use on IL-6 ($p = .632$, 95% CI = −0.113 to 0.185).

Tumor Necrosis Factor α

Results showed that the three-way interaction between depressive symptoms, metformin use, and sample group was not significant for log-transformed TNF-α ($b = 0.001$, SE = 0.013, $p = .931$, 95% CI = −0.025 to 0.027, $f^2 = 0.08$). Metformin did not moderate the link between depressive symptoms and log-transformed TNF-α among those in MIDUS ($p = .518$, 95% CI = −0.015 to 0.030) and SALSA ($p = .369$, 95% CI = −0.007 to 0.020). Upon dropping the triple-interaction term, two-way interactions and main effects remained nonsignificant (*p* values > .106).

Supplemental Analyses

Secondary Covariates

Supplementary analyses showed the robustness of results after adding secondary covariates of smoking, steroid use,

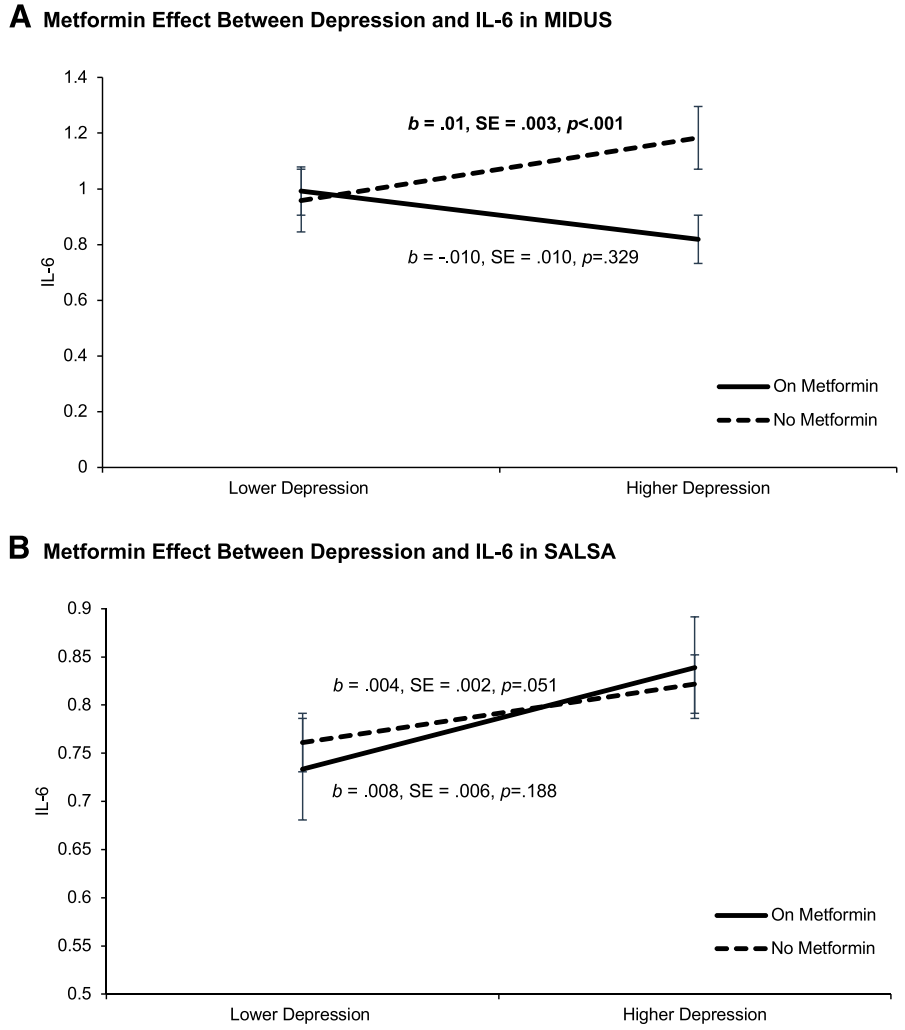

FIGURE 2. Associations of depressive symptoms with inflammatory marker IL-6 at different levels of metformin use in the MIDUS and SALSA samples. Parameter estimates (*b*), SEs, and *p* values are provided for each slope. Estimates in boldface are significant ($p < .05$). IL-6 = interleukin 6; MIDUS = Midlife in the United States Study; SALSA = Sacramento Area Latino Study on Aging; SE = standard error.

diabetes status, and minority status. There were no differences in the findings as a function of adding the secondary covariates. There was still a significant triple interaction between metformin use, depressive symptoms, and sample group membership for CRP ($b = 0.036$, SE = 0.013, $p = .004$) and IL-6 ($b = 0.024$, SE = 0.012, $p = .043$), but not TNF-α ($p = .983$). Metformin use significantly moderated the link between depressive symptoms and CRP ($b = 0.03$, SE = 0.011, $p = .006$) and IL-6 (b = 0.021, SE = 0.010, $p = .040$), respectively. Following the same pattern as the primary results, metformin did not moderate the link between depressive symptoms and TNF-α ($p = .525$).

Age Analyses

Supplemental analyses showed that the four-way interaction between depressive symptoms, metformin use, sample group, and age was not significant for log-transformed CRP ($p = .457$), IL-6 ($p = .849$), or TNF-α ($p = .269$). The nonsignificant four-way interaction term was removed in each inflammatory marker model, and the lower-order interactions were examined. There were no significant lower-order age effects for TNF-α (p values > .108).

The three-way interaction between age, metformin use, and depression did not significantly predict CRP ($p = .928$) or IL-6 ($p = .921$), indicating that age did not function as a significant moderator in both models. Moreover, the sample moderating effect, indicated by the only significant three-way interaction between sample group, metformin use, and depression, remained unchanged for both CRP ($p = .003$) and IL-6 ($p = .019$).

After the removal of the nonsignificant three-way interactions within the IL-6 model, a significant two-way interaction effect was observed between age and metformin use ($b = 0.018$, SE = 0.007, $p = .012$, 95% CI = 0.004–0.032, $f^2 = 0.18$). Simple slope analyses revealed that among individuals not taking metformin, advancing age was associated with increased IL-6 ($b = 0.021$, SE = 0.002, $p < .001$). Conversely, age was not significant among participants taking metformin ($b = 0.003$, SE = 0.007, $p = .688$). This pattern was not shown in the CRP model, as the two-way interaction between age and metformin use was not significant ($p = .138$).

Within the IL-6 model, a significant two-way interaction effect between sample group and age was detected ($b = 0.013$, SE = 0.004, $p < .001$, 95% CI = 0.006–0.020, $f^2 = 0.18$). Older adults had higher IL-6 among both samples, but this effect was stronger in SALSA ($b = 0.027$, SE = 0.003, $p < .001$) compared with MIDUS ($b = 0.014$, SE = 0.002, $p < .001$). This two-way interaction was not significant in the CRP model ($p = .669$).

DISCUSSION

In a national sample of midlife and older Americans, metformin buffered the link between depressive symptoms, a well-known behavioral risk factor, and inflammation, a key hallmark of biological aging, in two inflammatory markers—CRP and IL-6. However, in a large sample of older Mexican Americans, metformin usage did not exhibit a protective role. Furthermore, the significance of the three-way interaction underscores the importance of considering the sample group in understanding the relationship between depression, metformin use, and inflammatory levels. The specific characteristics or circumstances of the sample groups (e.g., different demographic profiles or health conditions) may contribute to the observed interaction effects. On the one hand, these findings uncover the potential for metformin to disrupt the risky tie between depressive symptoms and systemic inflammation, and thus may further bolster its promise for healthy aging. On the other hand, the null results among older Mexican Americans raise questions about whether people in historically underserved communities and those of ethnic minority groups will reap the potential benefit.

Consistent with hypotheses, among metformin nonusers in the MIDUS study, greater depression was significantly associated with higher CRP and IL-6. This pattern replicates the firmly established association between depressive symptoms and inflammation (12,13). However, also as predicted, these associations were attenuated among metformin users. Metformin did not buffer against the association with TNF-α, in part because the main effect of depressive symptoms was nonsignificant.

These results that identified metformin as a significant moderator in the MIDUS study widen the scope of potential benefits metformin may carry. To date, metformin has been identified to act on biological aging pathways, inhibiting the mammalian target of rapamycin pathway, which leads to a reduction in inflammation and promotes longevity (66). Preclinical studies, including in animals and patient records, have also shown metformin's anti-inflammatory effects (7). Rapidly gaining momentum in the geroscience research community, metformin is the focus of ongoing clinical trials to confirm the safety and efficacy of its potential role in altering the pace of biological aging (5). Even beyond these main effects that metformin may have in lowering inflammation, this study's results suggest that metformin may also buffer against key psychosocial sources of inflammation such as depressive symptoms (12), a novel, unintended benefit of this therapeutic.

Critically, the moderating association that emerged in the MIDUS study was not observed in the SALSA sample. Indeed, among older Mexican Americans, the association between depression and inflammatory markers, CRP and IL-6, did not depend on metformin use. MIDUS and SALSA participants were strikingly similar in many ways. These two large samples featured similar average BMIs, numbers of men and women, proportions of metformin users, and proportions of diabetic and prediabetic patients among the metformin users. However, they differed widely on demographic factors, structural factors, and socioeconomic status (SES).

SALSA participants were much older (mean = 70.64 years) than MIDUS participants (mean = 57.36 years). Older adults often experience chronically elevated low-grade inflammation with increasing age, or inflammaging (8,67). SALSA, a sample that consists entirely of ethnic minorities, also had lower education levels compared with MIDUS participants who were mostly White.

Interestingly, there was a lack of significant associations between CRP and IL-6 with depressive symptoms in the SALSA sample. A prior study using data from another nationally representative sample (National Health and Nutrition Examination Survey) found that the association between depression and inflammation was only present in non-Hispanic White individuals, whereas no significant associations were observed in non-Hispanic Black, Mexican American, or other Hispanic individuals (68). Our findings emphasize the importance of further investigating the role of race/ethnicity as a moderator in depression-inflammation studies, supporting the need for more comprehensive research in this area.

Low SES and being a member of a minority group are considered to be among the social hallmarks of risk, a set of social factors that can "get under the skin" and impact age-related health outcomes, also termed *social hallmarks of aging* (41). The presence of compounding risk factors, including older age, minority status, and low SES, within the SALSA sample may diminish the potential anti-inflammatory benefit of metformin. To gain a deeper understanding of the underlying mechanisms, further investigation in future studies is essential. These investigations should focus on elucidating how these specific compounding risk factors, such as older age, minority status, and low SES, can impact the potential anti-inflammatory effects of metformin in the SALSA population. Groups characterized by social hallmarks of risk are aging quicker and dying younger (69). Although there may be a moderating effect of metformin on depression and inflammation in some populations, the findings of the present study indicate that this pattern of results is weaker and inconsistent across inflammatory indicators. This underscores the significance of taking into account individual and population-based variations as crucial factors for comprehending the interplay between various risk and protective elements in influencing the process of healthy aging (6,41). An implication that emerges from the current findings is the potential challenge of providing geroherapeutics, such as metformin, to disadvantaged groups. It suggests that, although these groups may have the greatest need for such interventions, the presence of social risk factors that contribute to biological aging could potentially diminish the benefits associated with these promising interventions. (41,69).

Supplemental age analyses provided crucial insights into the associations among age, metformin use, sample group, and their interactions within the IL-6 and CRP inflammatory marker models. In the harmonized sample, the three-way interaction between age, metformin use, and depression was not significant, indicating that the magnitude of the buffering effect was not significantly greater or smaller for older adults

compared with their younger or middle-aged counterparts. However, the sample moderating effect remained, suggesting that sample differences are not attributable to age alone. In both samples, a significant two-way interaction between age and metformin use replicated the well-established association between age and higher IL-6 levels, specifically among those not taking metformin. However, this effect was nonsignificant among metformin users, suggesting that metformin may buffer age-related inflammation, regardless of higher or lower depressive symptoms.

A limitation to consider in the context of this analysis is the uneven age and ethnicity distribution across the sample groups, particularly the overrepresentation of older participants in SALSA. Despite this, the age-related effect on IL-6 levels in both samples supports the presence of inflammaging, aligning with prior research highlighting a strong link between advancing age and heightened IL-6 levels (70–72). These divergent patterns suggest that the MIDUS-SALSA disparities go beyond age, possibly involving ethnicity or the intricate dynamics of being an older person of minority status. Nevertheless, studies with sufficient statistical power to disentangle the effects of age, ethnicity, and their intersection need to further explore this question.

The most important limitation of this study is the cross-sectional nature of the data obtained from the publicly available MIDUS and SALSA datasets (52,54). This study design prevents us from establishing a causal relationship and understanding the dynamic changes that occur over time. Longitudinal follow-up studies are necessary to examine the effects of aging on the associations observed, including the long-term impact of metformin use, the trajectory of inflammatory markers, and the interplay between depressive symptoms and these factors. By incorporating longitudinal data, we can gain a deeper understanding of the complex relationships between metformin use, inflammation, depressive symptoms, and aging processes. Nevertheless, the current study provokes many important and provocative research questions to pursue in the future. Off-label metformin use has exploded in recent years; thus, incorporating more recent waves of data may show an increase in the subsample of metformin users. The current samples did not have enough individuals taking metformin to probe effects of dose and combinations of metformin with other drugs. We also did not have information on medication adherence or barriers to adherence, such as lack of transportation to obtain refills or payment for medication. Other potential social barriers that may impact aging-related health outcomes like inflammation, such as reduced access to health care and acculturative stress, should also be considered in future research.

Another notable limitation of this study is the challenge posed by the differences in measurement across both samples, which were derived from two separate studies. These variations in measurement and data collection processes may introduce potential discrepancies and affect the comparability between the cohorts. For example, education, which serves as a proxy for SES, was measured differently between the MIDUS and SALSA datasets. In MIDUS, education was measured categorically, whereas in SALSA, it was measured continuously. These discrepancies prevented the inclusion of education as a covariate in the harmonized sample. The inability to include education as a covariate hinders our ability to fully account for the potential confounding effects of SES on the observed associations. Education is a crucial indicator of socioeconomic disparities and plays a significant role in health outcomes. Its omission as a covariate limits our understanding of the influence of SES on the relationships between metformin use, inflammation, depressive symptoms, and aging processes. To evaluate education as a covariate, we performed supplementary analyses within each sample (nonharmonized). These analyses confirmed consistent patterns of metformin's buffering effect on CRP and IL-6, and not TNF-α, in MIDUS. Moreover, no buffering effect was observed in SALSA for all three inflammatory markers (see Supplemental Digital Content, http://links.lww.com/PSYMED/A976). Future research should strive to overcome this limitation by using datasets with consistent measurements of education or by using other valid measures of SES to capture its impact on the associations under investigation. By including a comprehensive assessment of SES, researchers can better explore the complex interplay between socioeconomic factors, metformin use, inflammation, and depressive symptoms in relation to aging.

This study showed that metformin may have a mitigating role in the link between depression and inflammation in mostly White, highly educated adults. However, the results were mixed, as the benefits did not extend to Latino older adults significantly. The two samples were similar in several ways (BMI, sex demographics, proportion of metformin users, and their diabetes status), except that the group of Latino older adults differed in biological and social hallmarks of risk (older age, minority status, lower education attainment). It is possible that metformin may work differently across varying subgroups, a question needing further exploration in future studies. In sum, the findings of this study point to additional benefits of metformin as a therapeutic agent for aging-related chronic diseases, but also raise important questions about its capacity to promote health equity among diverse population groups.

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REFERENCES

1. Brinkley TE, Leng X, Miller ME, Kitzman DW, Pahor M, Berry MJ, et al. Chronic inflammation is associated with low physical function in older adults across multiple comorbidities. J Gerontol A Biol Sci Med Sci 2009;64:455–61.
2. Fulop T, Larbi A, Witkowski JM, McElhaney J, Loeb M, Mitnitski A, et al. Aging, frailty and age-related diseases. Biogerontology 2010;11:547–63.
3. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. Nat Med 2019;25:1822–32.
4. Barzilai N, Cuervo AM, Austad S. Aging as a biological target for prevention and therapy. JAMA 2018;320:1321–2.
5. Barzilai N, Crandall JP, Kritchevsky SB, Espeland MA. Metformin as a tool to target aging. Cell Metab 2016;23:1060–5.
6. Epel ES. The geroscience agenda: toxic stress, hormetic stress, and the rate of aging. Ageing Res Rev 2020;63:101167.
7. Justice JN, Gubbi S, Kulkarni AS, Bartley JM, Kuchel GA, Barzilai N. A geroscience perspective on immune resilience and infectious diseases: a potential case for metformin. GeroScience 2021;43:1093–112.

8. Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES, et al. Geroscience: linking aging to chronic disease. Cell 2014;159:709–13.
9. Sierra F. The emergence of geroscience as an interdisciplinary approach to the enhancement of health span and life span. Cold Spring Harb Perspect Med 2016;6:a025163.
10. Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, et al. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med 2013;11:200.
11. Cyranowski JM, Marsland AL, Bromberger JT, Whiteside TL, Chang Y, Matthews KA. Depressive symptoms and production of proinflammatory cytokines by peripheral blood mononuclear cells stimulated in vitro. Brain Behav Immun 2007;21:229–37.
12. Kiecolt-Glaser JK, Derry HM, Fagundes CP. Inflammation: depression fans the flames and feasts on the heat. Am J Psychiatry 2015;172:1075–91.
13. Mac Giollabhui N, Ng TH, Ellman LM, Alloy LB. The longitudinal associations of inflammatory biomarkers and depression revisited: systematic review, meta-analysis, and meta-regression. Mol Psychiatry 2021;26:3302–14.
14. Moffitt TE. Behavioral and social research to accelerate the geroscience translation agenda. Ageing Res Rev 2020;63:101146.
15. Bai B, Chen H. Metformin: a novel weapon against inflammation. Front Pharmacol 2021;12:622262.
16. Kulkarni AS, Gubbi S, Barzilai N. Benefits of metformin in attenuating the hallmarks of aging. Cell Metab 2020;32:15–30.
17. Martin-Montalvo A, Mercken EM, Mitchell SJ, Palacios HH, Mote PL, Scheibye-Knudsen M, et al. Metformin improves healthspan and lifespan in mice. Nat Commun 2013;4:2192.
18. Anisimov VN, Berstein LM, Popovich IG, Zabezhinski MA, Egormin PA, Piskunova TS, et al. If started early in life, metformin treatment increases life span and postpones tumors in female SHR mice. Aging 2011;3:148–57.
19. Mair W, Morantte I, Rodrigues APC, Manning G, Montminy M, Shaw RJ, et al. Lifespan extension induced by AMPK and calcineurin is mediated by CRTC-1 and CREB. Nature 2011;470:404–8.
20. Mohammed I, Hollenberg MD, Ding H, Triggle CR. A critical review of the evidence that metformin is a putative anti-aging drug that enhances healthspan and extends lifespan. Front Endocrinol 2021;12:718942.
21. Onken B, Driscoll M. Metformin induces a dietary restriction-like state and the oxidative stress response to extend *C. elegans* Healthspan via AMPK, LKB1, and SKN-1. PLoS One 2010;5:e8758.
22. Cameron AR, Morrison VL, Levin D, Mohan M, Forteath C, Beall C, et al. Anti-inflammatory effects of metformin irrespective of diabetes status. Circ Res 2016;119:652–65.
23. Liu Z, Yu X, Tong C, Qi H. Renal dysfunction in a mouse model of GDM is prevented by metformin through MAPKs. Mol Med Rep [Internet] 2019;19:4491–9. Available at: http://www.spandidos-publications.com/10.3892/mmr.2019.10060. Accessed January 22, 2023].
24. Dziubak A, Wójcicka G, Wojtak A, Bełtowski J. Metabolic effects of metformin in the failing heart. Int J Mol Sci 2018;19:2869.
25. Wu H, Huang D, Zhou H, Sima X, Wu Z, Sun Y, et al. Metformin: a promising drug for human cancers. Oncol Lett 2022;24:204.
26. Isoda K, Young JL, Zirlik A, MacFarlane LA, Tsuboi N, Gerdes N, et al. Metformin inhibits proinflammatory responses and nuclear factor-κB in human vascular wall cells. Arterioscler Thromb Vasc Biol 2006;26:611–7.
27. Nerstedt A, Johansson A, Andersson CX, Cansby E, Smith U, Mahlapuu M. AMP-activated protein kinase inhibits IL-6–stimulated inflammatory response in human liver cells by suppressing phosphorylation of signal transducer and activator of transcription 3 (STAT3). Diabetologia 2010;53:2406–16.
28. Zhang ZJ, Yuan J, Bi Y, Wang C, Liu Y. The effect of metformin on biomarkers and survivals for breast cancer—a systematic review and meta-analysis of randomized clinical trials. Pharmacol Res 2019;141:551–5.
29. Amoani B, Sakyi SA, Mantey R, Laing EF, Ephraim RD, Sarfo-Katanka O, et al. Increased metformin dosage suppresses pro-inflammatory cytokine levels in systemic circulation and might contribute to its beneficial effects. J Immunoassay Immunochem 2021;42:252–64.
30. Kamyshnyi O, Matskevych V, Lenchuk T, Strilbytska O, Storey K, Lushchak O. Metformin to decrease COVID-19 severity and mortality: molecular mechanisms and therapeutic potential. Biomed Pharmacother 2021;144:112230.
31. Cheng X, Liu YM, Li H, Zhang X, Lei F, Qin JJ, et al. Metformin is associated with higher incidence of acidosis, but not mortality, in individuals with COVID-19 and pre-existing type 2 diabetes. Cell Metab 2020;32:537–547.e3.
32. Drzewoski J, Hanefeld M. The current and potential therapeutic use of metformin-the good old drug. Pharm Basel Switz 2021;14:122.
33. Le S, Lee GC. Emerging trends in metformin prescribing in the United States from 2000 to 2015. Clin Drug Investig 2019;39:757–63.
34. Piskovatska V, Stefanyshyn N, Storey KB, Vaiserman AM, Lushchak O. Metformin as a geroprotector: experimental and clinical evidence. Biogerontology 2019;20:33–48.
35. Kristófi R, Eriksson JW. Metformin as an anti-inflammatory agent: a short review. J Endocrinol 2021;251:R11–22.
36. Saisho Y. Metformin and inflammation: its potential beyond glucose-lowering effect. Endocr Metab Immune Disord Drug Targets 2015;15:196–205.
37. Pradhan AD, Everett BM, Cook NR, Rifai N, Ridker PM. Effects of initiating insulin and metformin on glycemic control and inflammatory biomarkers among patients with type 2 diabetes: the LANCET randomized trial. JAMA 2009;302:1186–94.
38. Sobel BE, Hardison RM, Genuth S, Brooks MM, McBane RD, Schneider DJ, et al. Profibrinolytic, antithrombotic, and antiinflammatory effects of an insulin-sensitizing strategy in patients in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. Circulation 2011;124:695–703.
39. Manigault AW, Ganz PA, Irwin MR, Cole SW, Kuhlman KR, Bower JE. Moderators of inflammation-related depression: a prospective study of breast cancer survivors. Transl Psychiatry 2021;11:615.
40. Straka K, Tran ML, Millwood S, Swanson J, Kuhlman KR. Aging as a context for the role of inflammation in depressive symptoms. Front Psych 2020;11:605347.
41. Crimmins EM. Social hallmarks of aging: suggestions for geroscience research. Ageing Res Rev 2020;63:101136.
42. Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, et al. Inflamm-aging: an evolutionary perspective on immunosenescence. Ann N Y Acad Sci 2006;908:244–54.
43. Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, Sevini F, et al. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mech Ageing Dev 2007;128:92–105.
44. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci 2014 Jun 1;69(Suppl 1):S4–9.
45. Liu C, Foti K, Grams ME, Shin JI, Selvin E. Trends in self-reported prediabetes and metformin use in the USA: NHANES 2005–2014. J Gen Intern Med 2020;35:95–101.
46. Diabetes Prevention Program Research Group, Crandall J, Schade D, Ma Y, Fujimoto WY, Barrett-Connor E, Fowler S, et al. The influence of age on the effects of lifestyle modification and metformin in prevention of diabetes. J Gerontol A Biol Sci Med Sci 2006;61:1075–81.
47. Zenebe Y, Akele B, W/Selassie M, Necho M. Prevalence and determinants of depression among old age: a systematic review and meta-analysis. Ann Gen Psychiatry 2021;20:55.
48. Zurlo KA, Beach CM. Racial disparities in depression care among older adults: can the perspectives of clinicians and patients be reconciled? Curr Transl Geriatr Exp Gerontol Rep 2013;2:24–30.
49. Fiske A, Wetherell JL, Gatz M. Depression in older adults. Annu Rev Clin Psychol 2009;5:363–89.
50. Fiske A, Gatz M, Pedersen NL. Depressive symptoms and aging: the effects of illness and non–health-related events. J Gerontol B Psychol Sci Soc Sci 2003;58:P320–8.
51. Brim OG, Ryff CD, Kessler RC, editors. How Healthy Are We? A National Study of Well-Being at Midlife. Chicago, IL: University of Chicago Press; 2004:687 (The John D. and Catherine T. MacArthur Foundation series on mental health and human development. Studies on successful midlife development).
52. Ryff CD, Seeman T, Weinstein M. Midlife in the United States (MIDUS 2): Biomarker Project, 2004–2009: Version 9 [Internet]. ICPSR—Interuniversity Consortium for Political and Social Research; 2010. Available at: https://www.icpsr.umich.edu/web/NACDA/studies/29282/versions/V9. Accessed January 18, 2023.
53. Dienberg Love G, Seeman TE, Weinstein M, Ryff CD. Bioindicators in the MIDUS national study: protocol, measures, sample, and comparative context. J Aging Health 2010 Dec;22:1059–80.
54. Haan M, Aiello A, Gonzalez H, Hinton L, Jagust B, Miller J, et al. Sacramento Area Latino Study on Aging (SALSA Study), 1996–2008: Version 1 [Internet]. ICPSR—Interuniversity Consortium for Political and Social Research; 2009. Available at: https://www.icpsr.umich.edu/web/NACDA/studies/22760/versions/V1. Accessed January 18, 2023.
55. Guarnaccia PJ, Angel R, Worobey JL. The factor structure of the CES-D in the Hispanic health and nutrition examination survey: the influences of ethnicity, gender and language. Soc Sci Med 1989;29:85–94.
56. Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. Psychol Aging 1997;12:277–87.
57. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Measur 1977;1:385–401.
58. DeSilva B, Smith W, Weiner R, Kelley M, Smolec J, Lee B, et al. Recommendations for the bioanalytical method validation of ligand-binding assays to support pharmacokinetic assessments of macromolecules. Pharm Res 2003;20:1885–900.
59. Haan M, Mungas DM, Gonzalez HM, Ortiz TA, Acharya A, Jagust WJ. Prevalence of dementia in older Latinos: the influence of type 2 diabetes mellitus, stroke and genetic factors. J Am Geriatr Soc 2003;51:169–77.
60. Aiello AE, Haan M, Pierce CM, Simanek AM, Liang J. Persistent infection, inflammation, and functional impairment in older Latinos. J Gerontol A Biol Sci Med Sci 2008;63:610–8.
61. Shih IF, Haan M, Paul KC, Yu Y, Sinsheimer JS, Ritz B. The roles of physical activity and inflammation in mortality, cognition, and depressive symptoms among older Mexican Americans. Am J Epidemiol 2019;188:1944–52.
62. American Diabetes Association. (2) Classification and Diagnosis of Diabetes. Diabetes Care 2015;38(Suppl 1):S8–16.
63. Bennett JM, Glaser R, Malarkey WB, Beversdorf DQ, Peng J, Kiecolt-Glaser JK. Inflammation and reactivation of latent herpesviruses in older adults. Brain Behav Immun 2012;26:739–46.
64. Mac Giollabhui N, Ellman LM, Coe CL, Byrne ML, Abramson LY, Alloy LB. To exclude or not to exclude: considerations and recommendations for C-reactive protein values higher than 10 mg/L. Brain Behav Immun 2020;87:898–900.
65. Trichopoulos D, Psaltopoulou T, Orfanos P, Trichopoulou A, Boffetta P. Plasma C-reactive protein and risk of cancer: a prospective study from Greece. Cancer Epidemiol Biomarkers Prev 2006;15:381–4.
66. Cheng FF, Liu YL, Du J, Lin JT. Metformin's mechanisms in attenuating hallmarks of aging and age-related disease. Aging Dis 2022;13:970–86.

67. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol 2018;15:505–22.
68. Stewart JC. One effect size does not fit all—is the depression-inflammation link missing in racial/ethnic minority individuals? JAMA Psychiatry 2016;73:301–2.
69. Sierra F, Caspi A, Fortinsky RH, Haynes L, Lithgow GJ, Moffitt TE, et al. Moving geroscience from the bench to clinical care and health policy. J Am Geriatr Soc 2021;69: 2455–63.
70. Maggio M, Guralnik JM, Longo DL, Ferrucci L. Interleukin-6 in aging and chronic disease: a magnificent pathway. J Gerontol Ser A 2006;61:575–84.
71. Said EA, Al-Reesi I, Al-Shizawi N, Jaju S, Al-Balushi MS, Koh CY, et al. Defining IL-6 levels in healthy individuals: a meta-analysis. J Med Virol 2021;93:3915–24.
72. Minciullo PL, Catalano A, Mandraffino G, Casciaro M, Crucitti A, Maltese G, et al. Inflammaging and anti-inflammaging: the role of cytokines in extreme longevity. Arch Immunol Ther Exp (Warsz) 2016;64:111–26.