Executive Functioning and Diabetes: The Role of Anxious Arousal and Inflammation

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Highlights

- The executive function of inhibition is associated with diabetes.
- Higher inhibition is associated with lower inflammation.
- The serial pathway from anxious arousal to inflammation explained the association between inhibition and diabetes.
Abstract

Individuals who perform poorly on measures of the executive function of inhibition have higher anxious arousal in comparison to those with better performance. High anxious arousal is associated with a pro-inflammatory response. Chronically high anxious arousal and inflammation increase one’s risk of developing type 2 diabetes. We sought to evaluate anxious arousal and inflammation as underlying mechanisms linking inhibition with diabetes incidence. Participants \((N = 835)\) completed measures of cognitive abilities, a self-report measure of anxious arousal, and donated blood to assess interleukin-6 (IL-6) and glycated hemoglobin (HbA1c). Individuals with low inhibition were more likely to have diabetes than those with high inhibition due to the serial pathway from high anxious arousal to IL-6. Findings remained when entering other indicators of cognitive abilities as covariates, suggesting that inhibition is a unique cognitive ability associated with diabetes incidence. On the basis of our results, we propose several avenues to explore for improved prevention and treatment efforts for type 2 diabetes.

*Key words*: executive functioning, inhibition, anxious arousal, inflammation, diabetes
1. Introduction

Emotional stress is a risk factor for poor physical health. Indeed, high anxiety is associated with diabetes incidence (Li et al., 2008). A better understanding of the association between anxiety and blood glucose is important given that approximately 347 million people worldwide have diabetes, which has imposed a growing economic strain on health care systems (Zhang et al., 2010). Moreover, approximately 90% of all diabetes is type 2, which can be prevented or delayed via lifestyle changes (e.g., physical activity, diet; Tuomilehto & Wolf, 1987; WHO, 2014) that are more difficult to achieve when stressed or anxious (Stults-Holehmainen & Sinha, 2014). Therefore, a further understanding of the association between anxiety and blood glucose is needed to improve interventions. The present study draws from the psychoneuroimmunology literature to examine how cognitive processes and immune functioning underlie the association between anxious arousal and glycated hemoglobin (HbA1c), a well-known biomarker used to estimate blood glucose during the preceding 2-3 months.

The executive function of inhibition (also known as attentional control or inhibitory control) is associated with the experience of stressful emotions such as anxiety. Inhibition is the ability to refrain from responding or attending to tempting/distracting information, objects, thoughts, or activities. Indeed, those who have low inhibition are more likely to attend to anxious thoughts, and have greater difficulty shifting their attention away from such thoughts, than those with high inhibition (DeGutis et al., 2015; Joormann & Gotlib, 2010; Schmeichel & Tang, 2015). Others have argued that better inhibition is associated with less anxiety via the ability to flexibly and adaptively respond to one’s environment using optimal coping strategies (e.g., Martel, Nokolas, & Nigg, 2007). Indeed, inflexibility in thinking is associated with increased anxiety (e.g., Britton et al., 2010), which may explain why those with better inhibition report less anxiety than those with poor inhibition. The neurovisceral integration model (e.g., Thayer & Lane, 2009) also indicates that those with poor inhibition are less physiologically capable of responding and adapting to their environment in comparison to those with better inhibition. As a result, those
with poor inhibition are more likely to have a pre-attentive bias to threat information than those with better inhibition due to an inability to flexibly respond, and are more likely to report increased arousal due to this bias (Thayer & Friedman, 2004). Therefore, both cognitive and physiological processes may link poor inhibition with increased anxiety. High anxiety is associated with poor overall physical health in adults (Needham, Mezuk, Bareis, Lin, Blackburn, & Epel, 2015), which is notable given that those with low inhibition as children exhibit poor physical health outcomes in adulthood (Moffitt et al., 2011).

The underlying mechanisms linking low inhibition and poor health have not been adequately studied. In addition to increased anxiety (Schmeichel & Tang, 2015), low inhibition is also a risk factor for poor diabetes management because of an inability to consistently adhere to and complete diabetes management tasks (Wasserman, Hilliard, Schwartz, & Anderson, 2015). Therefore, it is important to generate a further understanding of how inhibition is linked to diabetes to improve prevention and intervention efforts.

Inflammation may play an important role in linking inhibition and diabetes. Those with high stress demonstrate a greater inflammatory response than individuals who are less stressed at the moderate effect size level (i.e., $r = .42$ to $0.57$; Fagundes, Glaser, Hwang, Malarkey, & Kiecolt-Glaser, 2013). Anxiety, as well as stress more generally, leads to inflammation via activation of nuclear factor-kappa B (NF-KB). Activation of NF-KB increases production of pro-inflammatory cytokines such as interleukin-6 (Bierhaus et al., 2003). Further, chronic inflammation is a reliable predictor of diabetes onset at the small effect size level (i.e., $r = .28$ to $0.33$; Chen et al., 2009; Perticone et al., 2008; Weng et al., 2010), as well as morbidity and mortality with small to moderate effect sizes typically identified (i.e., $r = .10$ to $0.40$; Kiecolt-Glaser, Gouin, & Hantsoo, 2010). In addition to inflammation being a predictor of diabetes onset, diabetes progression is associated with increased inflammation over time (Stehouwer et al., 2002). Chronic elevated inflammation is associated with increased risk of heart disease ($OR = 1.45$; Hansson, 2005), a major complication of diabetes (Grundy et al., 1999). Indicators of
anxious arousal (e.g., racing heart, chest pain) are stronger predictors of inflammation than cognitive anxiety (e.g., fearful of dying or losing control) at the small effects size level \((r = .12;\) Duivis, Vogelzangs, Kupper, de Jonge, & Penninx, 2013), possibly due to activation of the sympathetic nervous system (Janig, 2014).

As low inhibition is associated with high anxious arousal at the medium effect size level \((r = .38;\) DeGutis et al., 2015), low inhibition may also be associated with high inflammation; however, it is unclear if inhibition is associated with inflammation in the general population as the literature has primarily been focused on the natural decline of cognitive skills and increase in inflammation near the end of human life (Magaki, Mueller, Dickson, & Kirsch, 2007; Simen, Bordner, Martin, Moy, & Barry, 2011). Furthermore, inhibition is typically combined with other cognitive abilities in statistical analyses, limiting the ability to understand the unique effects of inhibition (Marsland et al., 2015). Specifically, indicators of executive functioning (i.e., working memory, cognitive flexibility, and inhibition) are often combined into a latent construct of executive functioning as opposed to being evaluated as individual predictors of targeted outcomes. Accordingly, it is important to determine if inhibition is associated with diabetes through anxious arousal and inflammation.

We expected that low inhibition would be associated with high anxious arousal and, in turn, high inflammation. It was predicted that the serial pathway from anxious arousal to inflammation would explain the association between inhibition and diabetes incidence (i.e., serial mediation). Furthermore, we expected that this pathway would remain significant above and beyond other indicators of cognitive abilities (i.e., performance on digit span, backwards counting, and number series measures).

2. Material and methods

2.1 Participants and procedure

Data were obtained from the Midlife Development in the United States (MIDUS) study in which mental and physical health outcomes were examined among a nationally representative
sample of middle aged adults. Data from two time points were utilized in the present study. Specifically, measures of cognitive ability described below were completed during a baseline visit. All other measures were completed at the follow-up visit, which occurred an average of 23.39 months ($SD = 14.28$) after participants completed cognitive measures. A total of 4,512 participants completed cognitive assessments. Of those who completed the cognitive assessments, a 1,255 agreed to participant, and were identified as being medically safe to travel to Madison, WI, Los Angeles, CA, or Washington, DC, for the follow-up assessment. Complete data was obtained from a total of 835 participants ($M_{age} = 57.62, SD = 11.60$). Significant mean differences were not identified among those with complete vs. incomplete data for the vast majority of study variables (i.e., inhibition, anxious arousal, interleukin-6, diabetes incidence, age, sex, ethnicity, body mass index, and time lag between assessments); however, participants with incomplete data were older ($t = 2.34, p = .02$) and more likely to have a history of smoking ($t = 2.84, p = .01$) in comparison to those with complete data, consistent with the need to be medically safe to travel to the follow-up assessment.

All cognitive tests were administered over the telephone in the MIDUS study (Tun & Lachman, 2006). The reliability and validity of conducting the cognitive measures over the phone in the MIDUS study was recently evaluated and excellent test-retest reliability was identified (Lachman et al., 2014). Moreover, moderate to large correlations ranging from .55 to .95 were identified between a telephone administration and an in-person administration in a subsample of 30 participants. In addition, moderate to large correlations ranging from .42 to .54 were identified between measures on the telephone administration and participant performance for similar measures on the Boston Cognitive Battery (Lachman et al., 2014) which is administered in person.

2.2 Measures

2.2.1 Inhibition
The stop and go switch task (SGST) was designed to measure inhibition and attention shifting (Lachman, Agrigoroaei, Tun, & Weaver, 2014; Tun & Lachman, 2006, 2008) and consists of three conditions. In the first condition (i.e., normal), participants were asked to respond by stating “stop” when presented with the stimulus word “red” or “go” when presented with the stimulus word “green” across 20 trials. For the second condition (i.e., reverse), participants were instructed to state the word “go” when presented with the stimulus word “red” and “stop” when presented with the stimulus word “green” across 20 trials. In the third and final condition (i.e., mixed), participants were provided with a cue of either “normal” or “reverse” before being presented with a stimulus word across 32 trials. For example, if a participant was provided with the cue of “normal” and the stimulus word “green,” the correct response was “go”; however, if they were presented with the cue of “reverse” and the stimulus word “green,” the correct response was “stop.” Response latency for the SGST in the present study reflects the average time it took to correctly respond to each stimulus in the reverse and mixed condition. In the normal condition, inhibition skills are not utilized, and as such, response latency in the normal condition was not included in present study analyses. During follow-up analyses, we included the number of errors from each condition as additional indicators of inhibition to determine if there were any speed/error tradeoffs. Indicators of inhibition were reverse coded such that higher scores indicated better inhibition.

Using response latency as the primary indicator of inhibition, Lachman et al. (2014) demonstrated excellent psychometric characteristics for the SGST. For instance, response latency for the mixed condition of the SGST was moderately correlated (i.e., $r = .52$) with Task Switching from the Boston Cognitive Battery, a 90 minute in person assessment, using a subsample of MIDUS participants ($n = 299$) who also participated in the Boston Longitudinal Study (BOLOS; Miller & Lachman, 2000). The SGST was also tested in person among a subsample ($n = 30$) of participants who had also completed the measure over the telephone.
The correlation between the telephone and in person administrations of the SGST was .71 (Lachman et al., 2014).

### 2.2.2 Anxious Arousal

The 62 item version of the Mood and Anxiety Symptom Questionnaire (MASQ; Clark & Watson, 1991) was utilized to measure anxious arousal. On the MASQ, individuals reported the degree to which they experienced various feelings or sensations (e.g., “was short of breath”) during the previous week on a scale ranging from 1 (very slightly or not at all) to 5 (extremely). A total of 16 items comprise the anxious arousal scale, with the remaining items assessing general distress and anhedonia. In the present study, the reliability coefficient for the anxious arousal scale was acceptable (α = .75).

### 2.2.3 Interleukin-6

Serum IL-6 levels were evaluated via high-sensitivity enzyme-linked immunosorbent assay (ELISA) (Quantikine, R&D Systems, Minneapolis, MN) with a sensitivity of detection at 0.16 pg.mL. Values were log transformed to normalize the distribution of scores. IL-6 was selected as an indicator of inflammation as it has been linked with anxious arousal (O’Donovan et al., 2010) and type 2 diabetes (Doyle et al., 2013). Serum IL-6 is also a marker of acute and chronic stress (Kiecolt-Glaser et al., 2003). Moreover, animal work has demonstrated that vagus nerve stimulation, which is associated with improved inhibition (Thayer & Lane, 2009), reduces production of tumor necrosis factor (TNF)-alpha and IL-6 (Wang et al., 2004). Other immune biomarkers that were analyzed during the MIDUS study (i.e., C-Reactive protein, IL-6 receptor, E-selectin, intercellular adhesion molecule 1 (ICAM-1)) are not strongly linked with vagus nerve stimulation and stress regulation, two important mechanisms for the association between inhibition and IL-6 (Steptoe, Hamer, & Chida, 2007; Wang et al., 2004).

### 2.2.4 Hemoglobin HbA1c

An HbA1c assay was performed by Meriter Labs in Madison, WI using the Cobas Integra® analyzer (Roche Diagnostics, Indianapolis, IN). Percent HbA1c, which is represented
in the descriptions and analyses below, is determined by the quotient of HA1C by total hemoglobin. Higher scores represent worse glycemic control. Consistent with the International Expert Committee’s suggestions for using HbA1c to diagnose diabetes (The International Expert Committee, 2009), scores above 6.5% were considered to be consistent with a diagnosis of diabetes; however, the committee suggested that a repeat measurement of HbA1c is needed for diagnosis of diabetes if clinical symptoms and blood glucose levels below 200 mg/dl (11.1 mmol/l) are identified. A second measurement was not conducted for such individuals in the present study. In the analyses described below, diabetes incidence was defined as whether or not participants demonstrated HbA1c levels greater than 6.5% and/or self-reported using medication to manage diabetes.

2.2.5 Demographics

Participants provided self-reported age, gender, ethnicity, smoking history, and current use of insulin. Participant height and weight was measured in order to calculate body mass index (BMI).

2.2.6 Digit span

The backward digit span task from the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III; Wechsler, 1997) was also used as a covariate in the present study. The digit span task involved the participant listening to a series of numbers ranging from two to eight digits that increased in length as they progressed through the trials. After listening to the series of numbers, the participants were asked to repeat each series in the reverse order. Participants were given two separate opportunities, using a different order of digits, to provide the correct response for a given series length. The task was discontinued if the participant did not provide the correct response to a trial after two attempts for a given series length. The number of digits in the longest series correctly recalled was utilized as an indicator of digit span ability. The backward digit span task was chosen as a covariate in the present study as it is related to the
executive function of updating/monitoring of information in working memory (Hilbert, Nakagawa, Puci, Zech, & Bühner, 2015).

### 2.2.7 Backwards counting task

For 30 seconds, participants were asked to count backwards from 100 as quickly as possible. The number of correct responses was utilized as an indicator of processing speed, a covariate in the present study. The number of errors due to repeating or skipping numbers was subtracted from the total score. This measure was chosen as a covariate given that processing speed is a predictor of performance on cognitive measures associated with aging that is separate, but related, to inhibition (e.g., Baudouin, Clarys, Vanneste, Isingrini, 2009).

### 2.2.8 Number series task

Participants completed a number series task (Salthouse & Prill, 1987) which was utilized as a covariate. For this task, participants were presented five-number series, one at a time, and were asked to indicate the correct number that should appear next in the series. Total scores reflected the number of series completed correctly after a five trials. It has been argued that measures of fluid reasoning, such as number series tasks, are related to the majority of measures of executive functioning and intelligence (e.g., Unsworth et al., 2009). As a result, this measure was chosen as a covariate to determine if broad cognitive skills explain hypothesized associations. This is important given that anxiety symptoms associated with post-traumatic stress have been found to be specific to inhibition as opposed to general executive dysfunction (DeGutis et al., 2015).

### 2.3 Analytic strategy

SPSS statistical software (IBM, 2012) was utilized for all analyses. Moreover, the model represented in Figure 1 was tested using the PROCESS macro for SPSS (Hayes, 2013) which allows for evaluation of serial mediation. Indirect effects were evaluated using 5,000 bootstrap samples. An indirect effect is significant if the 95% confidence interval does not contain zero (Hayes, 2013). Mediation models reflect that one variable (i.e., the mediator) explains, or
partially explains, an association between an independent and dependent variable. Of note, mediation models can be tested without longitudinal data if hypotheses are theoretically driven (MacKinnon, 2008). Furthermore, in serial mediation models, it is hypothesized that one mediator is serially associated with another mediator, and that this chain explains, or partially explains, an association between an independent and dependent variable (e.g., Hayes, 2012). Importantly, the PROCESS macro automatically identifies dichotomous dependent variables, such as diabetes incidence in the present study, and utilizes logistic regression. Participant age, gender, ethnicity, BMI, smoking history, and the time lag between assessments were utilized as covariates. Additionally, participant performance on the cognitive tasks representing digit span, backwards counting, and number series were entered as covariates in follow-up analyses.

3. Results

Descriptive statistics are presented in Table 1 and bivariate correlations are presented in Table 2. As expected, better inhibition was associated with less anxious arousal, IL-6, diabetes incidence, and HbA1c. Moreover, all indicators of cognitive ability were significantly positively associated. Furthermore, in line with hypotheses, higher anxious arousal was associated with greater IL-6. As expected, higher IL-6 was associated with a greater likelihood of diabetes incidence and higher HbA1c. Interestingly, increased anxious arousal was associated with a higher BMI and likelihood of reporting a history of regular cigarette use. Moreover, greater IL-6 was associated with higher BMI, and worse performance on all measures of cognitive ability.

As seen in Figure 1, lower inhibition was associated with greater anxious arousal and plasma IL-6. Higher anxious arousal was also associated with greater IL-6. Furthermore, serial mediation was supported, indicating that the sequential pathway from anxious arousal to IL-6 explained the association between inhibition and diabetes incidence. Covariates significantly associated with diabetes incidence included participant age ($B = .53, p < .05$) and BMI ($B = .54, p < .05$), as well as the time lag between assessment time points ($B = -.28, p < .05$). Primary findings remained consistent when examining HbA1c as a continuous dependent variable with
insulin use included as a covariate (Figure 2), in addition to when adding the number of errors made during the reverse and mixed tasks as additional indicators of inhibition. Furthermore, serial mediation was not supported when the sequence was reversed such that IL-6 led to anxious arousal \((.0013, SE = .0013; 95\% CI = - .0005, .0054)\). We also examined if diabetes incidence was associated with inflammation through the pathway from anxious arousal to inhibition given that management of diabetes is associated with potentially anxiety providing situations (Duke & Harris, 2014). Results did not support this serial mediational pathway \((.0004, SE = .0006; 95\% CI = - .0001, .0027)\).

In follow-up analyses, digit span, backwards counting and number series performance were examined as covariates in the model depicted in Figure 1 to determine if primary findings were unique to inhibition. All significant paths, as well as indirect effects, remained. Moreover, better number series performance was associated with lower anxious arousal \((β = - .13, p < .05)\) and decreased likelihood of meeting criteria for diabetes \((B = - .35, p < .05)\); however, further analysis revealed that number series performance was not associated with diabetes incidence through anxious arousal \((- .0082, SE = .0163; 95\% CI = - .0434, .0224)\) or IL-6 \((- .0113, SE = .0122; 95\% CI = - .0452, .0051)\). Moreover, inhibition was the only cognitive skill directly associated with IL-6.

4. Discussion

Our findings indicate that those with better inhibition evidence lower anxious arousal, IL-6, and HbA1c, in addition to a lower likelihood of meeting criteria for diabetes, than those with poor inhibition. Additionally, those with higher anxious arousal had higher IL-6. As expected, higher IL-6 was associated with higher HbA1c and likelihood of diabetes incidence. In the full model (see Figure 1), poor inhibition was associated with increased diabetes incidence through the serial pathway from anxious arousal to IL-6 as hypothesized. These findings were unique to inhibition as outcomes did not change when other indicators of cognitive ability were included in the model. Findings extend the literature by demonstrating that low inhibition is a risk factor for
diabetes incidence as opposed to being a consequence of disease processes (e.g., Bottiroli et al., 2014; Tran, Baxter, Hamman, & Grigsby, 2014). Better number series performance was independently associated with lower anxious arousal and decreased likelihood of meeting criteria for diabetes, suggesting that number series performance and inhibition should be differentiated within models of diabetes incidence.

Parasympathetic nervous system and NF-κB activation are potential mechanisms linking inhibition with anxious arousal and inflammation. Indeed, those with poor inhibition are more likely to have stressful thoughts enter and continue to occupy working memory than those with better inhibition (Joorman, 2010). Moreover, those with poor inhibition are more likely to demonstrate maladaptive physiological and psychological responses to stressors than those with better inhibition (Lackschewitz, Hüther, & Kröner-Herwig, 2008). Therefore, as a result of being unable to block stressful thoughts from being attended to, and an inability to shift attention away from distressing thoughts, those with poor inhibition may be more likely to experience anxious arousal and demonstrate heightened inflammation when exposed to stressors than those with better inhibition. Although inhibition is a hypothesized precursor to anxious arousal and inflammation, further research is needed to evaluate if inhibition is associated with a general arousal system as opposed to being a precursor to anxious arousal and inflammation given this speculative hypothesis.

Maladaptive health behaviors associated with poor inhibition may also explain the association between inhibition and diabetes. Indeed, individuals with poor inhibition are less likely to eat healthy foods (Limbers & Young, 2015; Segerstrom & Nes, 2007) or engage in healthy amounts of physical activity than those with high inhibition, even when they have the intention of doing so (Hall, Fong, Epp, & Elias, 2008). Those with poor inhibition are less likely to consume fruits/vegetables (Allom & Mullan, 2014), adhere to a weight loss plan (Pauli-Pott, Özgür, Hebebrand, & Pott, 2010), utilize sunscreen (Allom, Mullan, & Sebastian, 2013), or demonstrate adaptive sleeping habits than those with better inhibition (Kor & Mullan, 2011).
Impaired inhibition also leads to alcohol relapse following treatment (Gardland, Franken, & Howard, 2012). High anxiety is also associated with poor health behaviors (e.g., diet, exercise; Bonnet et al., 2005). As high anxiety and poor health behaviors are known risk factors for type 2 diabetes (Li et al., 2008; WHO, 2014), future work should target health behaviors as an underlying mechanism linking inhibition with type 2 diabetes.

Findings point to several intervention opportunities that may reduce diabetes incidence. Mindfulness-based therapeutic techniques can improve neural networks associated with poor inhibition, such as in the anterior cingulate cortex (ACC; Gard et al., 2012) which facilitates executive attention by detecting and mitigating distracting thoughts (Van Veen & Carter, 2002). Low inhibition is also improved via stimulant medication (Rosch et al., 2015). Anxious arousal is reduced through cognitive behavioral therapy, and in particular, exposure and response prevention (Arch et al., 2013). Use of anti-inflammatory medication may also reduce risk of diabetes given present study findings (Serhan, Chiang, & Van Dyke, 2008). Further research is needed to determine if implementing such interventions can reduce diabetes incidence among at risk individuals.

Inhibition, anxious arousal, and inflammation are also important for diabetes management. Individuals with low inhibition are at risk for poor glycemic control leading to enhanced inhibition difficulties (Duke & Harris, 2014; Gailliot et al., 2007). Indeed, high blood glucose levels are associated with decreased inhibition (Flint & Turek, 2003). Furthermore, diabetes management is often associated with anxiety provoking behaviors (e.g., daily insulin self-injections, finger-pricks, social interactions) that are imperative to achieving optimal diabetes control (Snoek & Skinner, 2006). Anxious arousal contributes to avoidance of diabetes management behaviors (Kendzor et al., 2014). As a result, interventions designed to improve inhibition and/or decrease anxious arousal may also result in improved glycemic control.

The present study is limited given that IL-6 was the only immune marker available in the MIDUS study that is strongly linked with hypothesized mechanisms underlying the association
between inhibition and inflammation (e.g., Kiecolt-Glaser et al., 2003; Wang et al., 2004). We would expect similar findings if TNF-alpha was available and future studies would benefit from attempting to replicate present study findings using TNF-alpha as an additional marker of inflammation. The present study is also limited by the predominantly white sample and the reliance on self-report, in a yes or no question format, for whether or not participants were currently taking insulin for diabetes. Furthermore, the study did not include measurement of physical activity or other health behaviors outside of smoking. However, our findings are consistent with empirical and theoretical evidence linking inhibition, stress, and health (Rostamian et al., 2015) and we controlled for BMI, which is associated with the majority of health behaviors. Education may be important to consider in future work as the vast majority of the original MIDUS sample had at least a high school diploma (e.g., Tun & Lachman, 2008), which may have limited the variance in cognitive performance observed. Additionally, the present study is limited by measurement of inhibition an average of nearly two years prior to measurement of anxious arousal, inflammation, and HbA1c. Future work should examine how these associations change over time; however, it should be noted that inhibition skills have been found to be relatively stable over time (e.g., Ettenhofer, Hambrick, & Abeles, 2006; Harms, Zayas, Meltzoff, & Carlson, 2014), supporting present study findings. Moreover, as study variables were not assessed over multiple time points, directionality of associations cannot be determined. Longitudinal designs can address this limitation in future work.

5. Conclusions

Consistent with theoretical models linking inhibition, stress, and health, poor inhibition is associated with increased diabetes incidence through the serial pathway from high anxious arousal to high inflammation. These findings have important implications for the prevention and treatment of diabetes by identifying underlying mechanisms contributing to elevated blood glucose.

Contributors
K.W.M was involved in data analysis and manuscript writing for the present study. A.S.L, T.E.L., D.C.D, C.J.H, and C.P.F. provided critical feedback and edited the manuscript.

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**Table 1. Participant characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Met criteria for diabetes (n = 103)</th>
<th>Did not meet criteria for diabetes (n = 737)</th>
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<tr>
<td></td>
<td>Mean (SD) or number (%)</td>
<td>Mean (SD) or number (%)</td>
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<tr>
<td>Participant age at biological assessment</td>
<td>62.55 (10.88)</td>
<td>57 (11.58)</td>
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<td>Participant gender</td>
<td></td>
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<tr>
<td>Male</td>
<td>54 (52.4)</td>
<td>319 (43.6)</td>
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<tr>
<td>Female</td>
<td>49 (47.6)</td>
<td>413 (56.4)</td>
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<tr>
<td>Participant ethnicity</td>
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<tr>
<td>White</td>
<td>93 (90.3)</td>
<td>686 (93.8)</td>
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<tr>
<td>Non-white</td>
<td>10 (9.7)</td>
<td>46 (6.2)</td>
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<tr>
<td>Body mass index</td>
<td>32.51 (7.57)</td>
<td>28.69 (5.65)</td>
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<tr>
<td>Ever smoked cigarettes regularly?</td>
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<tr>
<td>Yes</td>
<td>51 (49.5)</td>
<td>428 (58.4)</td>
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<tr>
<td>No</td>
<td>52 (50.5)</td>
<td>304 (41.6)</td>
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<tr>
<td>Inhibition</td>
<td>-.21 (2.02)</td>
<td>.35 (1.94)</td>
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<tr>
<td>Log transformed interleukin-6</td>
<td>.45 (0.31)</td>
<td>.30 (0.32)</td>
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<td>Hemoglobin A1c percentage</td>
<td>7.53 (1.35)</td>
<td>5.73 (0.36)</td>
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<td>Fasting glucose mg/dL</td>
<td>133.22 (49.19)</td>
<td>95.16 (10.40)</td>
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<td>Digit span</td>
<td>4.71 (1.27)</td>
<td>5.08 (1.42)</td>
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<tr>
<td>Backwards counting</td>
<td>36.51 (11.45)</td>
<td>39.80 (10.82)</td>
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<tr>
<td>Number series</td>
<td>2.01 (1.40)</td>
<td>2.64 (1.50)</td>
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*Note. Inhibition reflects the z-standardization and combination of average reaction time and number of errors on the reversed and mixed conditions of the go-no go task.*
### Table 2. Bivariate correlations between study variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>1</th>
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<tr>
<td>1. Inhibition-reverse</td>
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<tr>
<td>2. Inhibition-mixed</td>
<td>.61*</td>
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*Note. Pearson correlations are presented for correlations between continuous variables; Spearman’s coefficients are presented for categorical variables. AA = anxious arousal; IL-6 = interleukin 6. Participant gender coded as 1 = male and 2 = female. Participant ethnicity coded as 0 = non-white and 1 = white. Smoking history coded as 0 = never smoked cigarettes regularly and 1 = have smoked cigarettes regularly. Current insulin use coded as 0 = no and 1 = yes. *p < .05.*
Table 3. Logistic regression analyses predicting diabetes incidence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
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</thead>
<tbody>
<tr>
<td>Inhibition</td>
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<td>-.01</td>
<td>-.04</td>
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<tr>
<td>Anxious Arousal</td>
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<td>.07</td>
<td>.04</td>
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<tr>
<td>Interleukin-6</td>
<td>.44*</td>
<td>.26*</td>
<td>.42*</td>
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</table>

*Note. Values represent logistic regression coefficients (i.e., odds ratios). Model 1 = unadjusted. Model 2 = adjusted for age, sex, ethnicity, body mass index, smoking history, and the time lag between cognitive and biological assessments. Model 3 = adjusted for performance on digit span, backwards counting and number series tasks. * p < .05*
Fig 1. A mediation model of associations between inhibition, anxious arousal, interleukin-6, and diabetes incidence. Standardized regression coefficients are represented when predicting anxious arousal and interleukin-6, while logistic regression coefficients are represented when predicting diabetes incidence. 95% confidence intervals are depicted in parentheses. Indirect effects using 5,000 bootstrap samples: anxious arousal (.0089, SE = .0144, 95% CI = -.0181, .0407), interleukin-6 (.0220, SE = .0142, 95% CI = .0023, .0616), and serial mediation (i.e., mediation in sequence; .0028, SE = .0022, 95% CI = .0003, .0103). Control variables included participant age, sex, ethnicity, body mass index, and smoking history, as well the time lag between assessments. * p < .05.
Anxious Arousal
Inhibition
Interleukin-6
HbA1c Percentage
- .08* (-.01, - .15)
.02 (- .03, .08)
- .12* (- .05, - .18)
- .08* (-.01, -.15)
- .01 (-.07, .04)
.02 (-.03, .08)
.06* (.01, .12)
- .12* (-.05, -.18)
.10* (.03, .17)

Fig 2. A mediation model of associations between inhibition, anxious arousal, interleukin-6, and HbA1c. Values represent standardized regression coefficients and 95% confidence intervals are depicted in parentheses. Indirect effects using 5,000 bootstrap samples: anxious arousal (- .0015, SE = .0038, 95% CI = -.0111, .0047), interleukin-6 (.0049, SE = .0034, 95% CI = .0005, .0154), and serial mediation (i.e., mediation in sequence; .0007, SE = .0006, 95% CI = .0001, .0028). Control variables included participant age, sex, ethnicity, body mass index, smoking history, insulin use, as well the time lag between assessments. * p < .05.
References


professionals from the American Heart Association. *Circulation, 100*(10), 1134-1146. doi: 10.1161/01.CIR.100.10.1134


