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BRIEF REPORT

Poor Glucose Regulation Is Associated With Declines in Well-Being Among Older Men, but Not Women

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Glucose regulation is a key aspect of healthy aging and has been linked to brain functioning and cognition. Here we examined the role of glucose regulation for within-person longitudinal trajectories of well-being. We applied growth models to data from the Berlin Aging Study II (N = 955), using insulin resistance as an index of glucoregulatory capacity. We found that poor glucose regulation (higher insulin resistance) was consistently associated with lower levels of well-being among older men but not women. Our study provides novel evidence for the relevance of glucose regulation for well-being among older men.

Keywords: aging, life satisfaction, insulin resistance, sex, Berlin Aging Study II

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This article reports data from the Berlin Aging Study II (BASE-II; co-principal investigators are Lars Bertram, Ilja Demuth, Denis Gerstorf, Ulman Lindenberger, Graham Pawelec, Elisabeth Steinhagen-Thiessen, and Gert G. Wagner).

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The study has not been presented at a conference or shared publicly.

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Well-being is often resistant to age-related declines and may even improve with advanced age (Scheibe & Carstensen, 2010). This phenomenon has been studied from motivational (Carstensen, 1995) and goal-striving perspectives (Heckhausen, Wrosch, & Schulz, 2019), but the role of physiological factors is less clear. Recent studies indicate that availability of energy resources (i.e., glucose) might be associated with well-being in old age. Specifically, glucose administration may protect older adults' preference for positive information under high cognitive load (the positivity effect; Mantantzis, Schlaghecken, & Maylor, 2017) and maintain positive affect after performing memory tasks of varying difficulty compared with placebo (Mantantzis, Maylor, & Schlaghecken, 2018). Whereas these studies have focused on glucose administration, we aim to examine the role of glucoregulatory capacity, a physiological factor implicated in healthy aging (e.g., Dahle, Jacobs, & Raz, 2009). Using longitudinal data from the Berlin Aging Study II (BASE-II), we examined the association of glucoregulatory capacity (insulin resistance) with within-person trajectories of three indicators of cognitive-evaluative aspects of well-being (satisfaction with life, life satisfaction, and morale) and the influence of sociodemographic, physical health, and cognitive characteristics as moderators.

The Nature and Correlates of Glucose Regulation

Glucose fuels numerous biological processes, with the human brain requiring up to 55% of circulating glucose to perform its daily functioning (Amiel, 1995). Glucose directly provides energy to the neurons and contributes to the synthesis of neurotransmitters including serotonin (Markus, 2008), a neurotransmitter associated with mood and well-being (Jenkins, Nguyen, Polglaze, & Bertrand, 2016). In fact, utilization of glycemic resources is critical for maintaining healthy brain function (Sünram-Lea & Owen, 2017). However, glucoregulatory efficiency drops considerably with advancing age at an estimated rate of 8% per decade (Blesa et al., 1997). Age-related declines in glucose regulation may contribute to cognitive decline (Geary, 2019; Messier, 2004), as suggested by associations between glucose regulation and cognition observed across cross-sectional (Messier, Tsiakas, Gagnon, & Desrochers, 2010) and longitudinal (Kong, Park, Lee, Cho, & Moon, 2018) studies. Although glucoregulatory capacity is associated with the ability to avoid both high and low levels of glucose, glucoregulatory decrements reflected in high glucose levels are strongly linked with cognitive deficits (e.g., Cherbuin, Sachdev, & Anstey, 2012).

One of the most common indices of glucoregulatory capacity in studies on aging is insulin resistance (Weinstein et al., 2015; Wolf, Tsenkova, Ryff, Davidson, & Willette, 2018). Insulin resistance is inferred from high levels of circulating insulin and is viewed as a sign that the cells require additional insulin for efficient glucose uptake (Chang & Halter, 2003). If insulin production does not meet the insulin demands, glucose levels might rise above normal values. Insulin is particularly important for brain health, and it contributes to a range of homeostatic and neuroprotective mechanisms (Blázquez, Velázquez, Hurtado-Carneiro, & Ruiz-Albusac, 2014). In fact, peripheral insulin resistance is associated with cerebral insulin dysregulations and can trigger cognitive decrements and depression (Banks, Owen, & Erickson, 2012). Interestingly, susceptibility to insulin resistance appears to be moderated by sex, with men exhibiting higher levels of insulin resistance

throughout adulthood than women (Varlamov, Bethea, & Roberts, 2015). This female advantage has been attributed to the protective effect of female sex hormones (e.g., estrogens), which may make older women less susceptible to developing insulin resistance (Clegg, 2012). Accordingly, studies have found cognitive performance of men, but not women, to be particularly vulnerable to glucoregulatory problems (Düzel et al., 2018; Mortby, Janke, Anstey, Sachdev, & Cherbuin, 2013), highlighting the role of sex-specific factors in glucose regulation and associated outcomes.

Associations between glucoregulatory capacity and older adults' well-being are poorly understood. Transient blood glucose elevation induced by glucose administration can preserve older adults' preference for positive over negative information under high cognitive demands (Mantantzis et al., 2017) and boost their positive affect after exertion on memory tasks (Mantantzis et al., 2018). Thus, the hypothesized link between glycemic resources and wellbeing in aging merits further investigation. Moreover, the ability to effectively utilize glycemic resources might contribute to preserved well-being in old age. Better glucoregulatory capacity has been associated with positive affect in older adults (Tsenkova, Love, Singer, & Ryff, 2007) and higher purpose in life among middle-aged adults (Boylan, Tsenkova, Miyamoto, & Ryff, 2017), whereas higher insulin resistance predicts greater susceptibility to negative affect in middle-aged samples (Wolf et al., 2018). Diabetes is also associated with increased depressive symptoms in middle-aged and older adults (Golden et al., 2008). These findings could reflect decrements in glucose metabolism affecting normal brain functions and health (Messier, 2004) and interfering with the synthesis of neurotransmitters that might support well-being (e.g., serotonin; Markus, 2008). Thus, older adults' ability to effectively utilize glycemic resources might moderate individual differences in trajectories of subjective well-being.

The Present Study

The present study investigated whether and how glucose regulation is associated with longitudinal trajectories of cognitiveevaluative well-being in old age that tap into global evaluations of different areas of life. We applied growth models to multiyear longitudinal data from BASE-II and used insulin resistance as an index of glucoregulation capacity. Our models also included sociodemographic, physical health, and cognitive variables as moderators. To comprehensively assess changes in subjective wellbeing, we used the Satisfaction with Life Scale (Diener, Emmons, Larsen, & Griffin, 1985), the life satisfaction item of the German Socioeconomic Panel (Fujita & Diener, 2005), and Lawton's (1975) morale scale. Considering the importance of glycemic resources for aspects of well-being, we expected higher insulin resistance to be associated with trajectories of low and progressively worsening well-being. Because men typically exhibit higher levels of insulin resistance than women (Clegg, 2012), we expected such associations to be particularly pronounced among older men than women.

Method

To address our research questions, we used longitudinal data from the BASE-II. An overview of the study design and data collection procedures can be found in previous publications (Ber206 MANTANTZIS ET AL.

tram et al., 2014; Gerstorf et al., 2016). Below, we provide details relevant to the current report.

Participants and Procedure

Participants were healthy, community-dwelling, older adults older than the age of 60 years, with available insulin resistance data and no diagnosis of diabetes. To minimize the influence of extreme glycemic values, we excluded participants with blood glucose values that are indicative of uncontrolled diabetes. The latter was determined via a standard oral glucose tolerance test, in which participants' blood glucose concentrations were assessed at baseline following overnight fasting and 2 hours after a 75-g glucose load (World Health Organization, 2006), and by glycated hemoglobin, which reflects the average glucose concentrations in the 2- to 3-month period preceding the assessment. Specifically, participants with fasting blood glucose levels ≥126 mg/dL, blood glucose after the 2-hr glucose challenge ≥200 mg/dL, or glycated hemoglobin ≥6.5% (see also Buchmann et al., 2016) were excluded from the analysis, leaving 1,437 older adults with available insulin resistance data in the sample.1 Comparisons between participants included versus excluded and analyses of sample attrition effects are in the online supplemental material. Ethics approval for BASE-II was granted by the ethics committees of the Charité University Hospital and the Max Planck Institute for Human Development (Berlin, Germany). The research questions examined here do not overlap with any previous BASE-II reports.

The well-being measures were obtained as part of a take-home questionnaire, using either an online interface or a paper-and-pencil format. Diener scale scores were collected in 2012–2013 and 2016, with N=1,259 and 224, respectively (two waves). Morale scale data were collected in 2012–2013, 2014, 2016, and 2017–2018, with $N=1,258,\,1,124,\,224,\,$ and 1,026, respectively (four waves). Life satisfaction (single item) scores were collected in 2008, 2009, 2010, 2012, 2012–2013, 2014, 2016, and 2017–2018, with $N=85,\,839,\,74,\,949,\,1,237,\,1,130,\,221,\,$ and 1,035, respectively (eight waves).

Measures

Well-being. To assess well-being, we used three measures tapping into cognitive-evaluative components of well-being. We used the Satisfaction with Life Scale (Diener et al., 1985; Cronbach's alpha = .84) in which participants rated five statements (e.g., "In most ways my life is close to my ideal") on a 5-point scale ranging from 1 (strongly disagree) to 5 (strongly agree) to indicate their level of agreement. Additionally, we used participants' ratings on the single item "How satisfied are you with your life, all things considered?" provided on a scale ranging from zero (completely unsatisfied) to 10 (completely satisfied). The item is widely used in psychological research (Headey, Muffels, & Wagner, 2010). We also used the morale subscale of the Philadelphia Geriatric Center Morale Scale (Lawton, 1975; Cronbach's alpha = .74). Participants were provided with three statements measuring life dissatisfaction (e.g., "I take things hard") and were instructed to respond on a scale ranging from 1 (strongly disagree) to 5 (strongly agree). Responses were reverse coded, such that higher scores indicate higher well-being. Scores were transformed to a standardized T metric (M = 50, SD = 10). Although these three

scales are designed to measure the same construct, cognitiveevaluative well-being, they differ in the number of items and the areas of life covered. Including three established well-being measures enabled testing the consistency and robustness of associations between glucose regulation and trajectories of well-being.

Glucose regulation. Participants' glucoregulatory capacity was assessed using the Homeostasis Model of Insulin Resistance (HOMA-IR; Matthews et al., 1985), calculated as Fasting Glucose (milligrams per deciliter) × Fasting Insulin (milliunits per milliliter)/405. The ability of the HOMA-IR to accurately assess levels of insulin resistance compared with clinical methods has been repeatedly documented (Wallace, Levy, & Matthews, 2004). Higher levels of HOMA-IR indicate higher insulin resistance and increased risk of decrements in glucoregulatory capacity.

Individual difference correlates. We considered the moderating role of sociodemographic, physical health, and cognitive characteristics. Sociodemographic variables included age (date of birth subtracted from each assessment's date), sex (0 = women, 1 = men), and education (years of formal schooling). Physical health variables included morbidity, based on participant-reported medical diagnoses and verified by medical examination as well as grip strength, a highly reliable index of functional health (Gale, Martyn, Cooper, & Sayer, 2007) assessed via a hand dynamometer, and body mass index (BMI). Cognitive functioning was assessed with the Digit Symbol Substitution test (Wechsler, 1981), an age-sensitive perceptual speed test (Hoyer, Stawski, Wasylyshyn, & Verhaeghen, 2004).

Statistical Analyses

To examine our research questions, we estimated growth models using multiyear longitudinal data on well-being. The model was specified as:

well-being_{ti} =
$$\beta_{0i} + \beta_{2i}(time-in-study_{ti}) + \beta_{4i}(time-in-study_{ti}^2) + e_{ti}$$
,

where person *i*'s well-being at occasion t, well-being_{ti}, is a function of an individual-specific intercept parameter, β_{0i} ; individual-specific linear and quadratic slope parameters, β_{2i} and β_{4i} ; and residual error, e_{ti} . The quadratic effect of time was included only if it was significantly different from zero. Following standard multilevel/growth modeling procedures (Ram & Grimm, 2015; Singer & Willett, 2003), individual intercepts, β_{0i} , and slopes, β_{2i} and β_{4i} , were modeled as a function of insulin resistance and the correlates. Interaction terms were tested but trimmed when not significant, always retaining the lower-order interactions if necessary. An example of the final model can be found in the online supplemental material. Interaction of the correlates with the quadratic change term were also tested and were kept in the model only if they were significant. Time in study was centered at the

¹ An additional 49 participants had a history of diabetes and/or prescription of antidiabetic medications. However, their laboratory values fell within the euglycemic range, indicating adequate glycemic control. Therefore, these participants were retained in the final sample. It should also be noted that diabetes diagnosis is part of the morbidity variable that is included as a covariate in the analyses, and inclusion of the participants carrying that diagnosis but exhibiting good glycemic control did not ignore that risk factor.

time point at which most data for each measure were collected (2012–2013 assessment for all well-being measures). Age was centered at 70 years and all other predictors were grand mean centered.

Models were fit to the data using SAS (SAS Institute Inc., Cary, NC, USA) PROC MIXED (Littell, Miliken, Stoup, & Wolfinger, 2006), with incomplete observations treated as missing at random (Little & Rubin, 1987). The sociodemographic, physical health, and cognitive variables used in the analyses also provide attrition-relevant information and thereby assist in addressing the longitudinal selectively in our outcomes (McArdle, 1994). Given the exploratory nature of our research questions, we are reporting all results with a significance level of p < .05.

Results

Glucose Regulation

Descriptive statistics and correlations among the variables can be found in the online supplemental material (Supplemental Tables 1 and 2). Higher insulin resistance was associated with lower satisfaction with life (Diener, r(1259) = -.08, p = .006; and single item, r(1237) = -.06, p = .033), male sex, r(1437) = .08, p = .002, lower educational attainment, r(1253) = -.11, p < .001, more morbidities, r(1323) = .14, p < .001, higher body mass index, r(1429) = .50, p < .001, and lower cognitive performance, r(1214) = -.07, p = .018.

Glucose Regulation and Trajectories of Well-Being

We estimated growth models to examine the role of insulin resistance and the correlates in shaping trajectories of well-being (see Table 1). Well-being was stable across measures, with steeper decline over time found only for the satisfaction with life scale (Diener, $\gamma_{20} = -0.63$, p = .005) and accelerated forms of decline for life satisfaction (single item, $\gamma_{40} = -0.03$, p = .047). Older age was associated with higher life satisfaction (single item, $\gamma_{01} = 0.21$, p = .002). Men evidenced lower levels of well-being on two of the three measures (Diener, $\gamma_{02} = -2.45$, p = .022; and single item, $\gamma_{02} = -2.26$, p = .009). In addition, several interaction effects for age, sex, and education were found for select well-being measures. Importantly, higher morbidity, lower grip strength, and

Table 1
Growth Curve Models of Well-Being Measures Over Time

Parameters	Satisfaction with life (Diener)		Life satisfaction (single item)		Well-being (morale)	
	Estimate	SE	Estimate	SE	Estimate	SE
Fixed effects						
Intercept _{v00}	50.02***	.32	50.22***	.26	49.85***	.26
$Time_{\gamma20}$	63**	.23	03	.05	13	.10
$Time_{\gamma40}^{220}$		_	03*	.01	_	_
$Age_{\sim 0.1}$.08	.08	.21**	.07	01	.07
Men _{v02}	-2.45^{*}	1.07	-2.26**	.86	91	.91
Education _{y03}	17	.11	12	.09	.01	.09
$Age \times Time_{\gamma 21}$	02	.06	02	.01	03	.03
$Men \times Time_{\gamma 22}$.01	.71	.12	.17	58	.36
Education \times Time _{$v23$}	.09	.08	01	.02	02	.04
$Age \times Men_{y04}$		_	.31*	.13	.56*	.22
$Men \times Education_{>05}$.45*	.22	_		_	_
Insulin resistance _{v06}	61 *	.25	37	.20	02	.22
Morbidity _{v07}	53*	.25	58**	.20	67**	.20
$Grip_{\gamma 08}$.30***	.06	.21***	.05	.21***	.05
$BMI_{\sim 09}$.05	.10	.03	.07	.04	.08
Digit symbol _{y010}	.08*	.03	.09**	.03	.09**	.03
Insulin resistance \times Time _{$\sqrt{26}$}	14	.15	04	.04	.09	.08
Morbidity \times Time _{27}	.01	.21	.05	.04	06	.08
$Grip \times Time_{\gamma 28}$.03	.04	01	.01	.01	.02
$BMI \times Time_{\gamma 29}$.02	.08	.01	.01	02	.03
Digit Symbol \times Time _{$\sqrt{30}$}	.02	.03	.001	.01	01	.01
Insulin Resistance × Men _{v011}			-1.45***	.35	-1.67**	.58
Insulin Resistance \times Grip _{$\gamma 012$}		_	_		.07*	.03
Insulin Resistance × Digit Symbol _{y013}		_	_		04*	.02
$Grip \times Age_{v014}$		_	_		03*	.01
$BMI \times Men_{v015}$	44**	.17	_		_	_
Random effects						
Variance intercept	72.14***	6.99	45.11***	2.58	44.14***	2.81
Variance time	1.46	2.55	.42***	.10	3.50***	.48
Covariance intercept, time	2.43	3.06	.40	.35	-3.41***	.77
Residual variance	18.12*	7.33	43.92***	1.26	42.71***	1.92

Note. BMI = body mass index; grip = grip strength. Unstandardized estimates are presented. N = 954 who provided 1,127 (satisfaction with life, Diener scale) and N = 955 who provided 4,186 (life satisfaction, single item) and 2,794 observations (well-being, morale), respectively. Scores were T standardized. Age centered at 70 years. Model parameters for insulin resistance as our focus variable highlighted in bold. p < .05. ** p < .01. *** p < .01.

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lower cognitive performance were associated with lower well-being, a pattern found consistently across all well-being measures: morbidity: Diener, $\gamma_{07} = -0.53$, p = .034; single item, $\gamma_{07} = -0.58$, p = .002; and morale, $\gamma_{07} = -0.67$, p = .001.

Higher insulin resistance was associated with lower satisfaction with life (Diener, $\gamma_{06} = -0.61$, p = .015). On the two other wellbeing measures, we found significant interactions between sex and insulin resistance (single item, $\gamma_{011} = -1.45$, p < .001; morale, $\gamma_{011} = -1.67$, p = .004), suggesting that higher insulin resistance was associated with lower well-being among men but not women (see Figure 1). Whereas no differences were found among older women, well-being was about 1 *SD* (approximately 10 T score units) lower among older men with high insulin resistance than among those at the lower end of the insulin resistance range (Figure 1, Panels B and C).

Finally, significant interactions between insulin resistance and grip strength, and insulin resistance and cognition were found for the morale scale ($\gamma_{012} = 0.07$, p = .025; $\gamma_{013} = -0.04$, p = .042, respectively), linking higher insulin resistance to lower well-being among participants with low grip strength and better cognitive performance.²

Discussion

Well-being is relatively stable across adulthood, but pronounced individual differences exist among older adults. The role of physiological factors in such heterogeneity is unclear. In the present study, we demonstrated that worse glucose regulation is consistently associated with lower well-being among older men but not older women. These findings were independent of sociodemographic and physical health characteristics. We argue that sex differences may moderate the associations between glucose regulation and well-being.

Our results point to the presence of sex-specific associations between glucose regulation and well-being, with women's well-being seemingly protected from the negative effects of insulin resistance. These findings could be attributed to the well-described sex differences in glucose regulation, such as lower insulin resistance in women compared with men (Camporez et al., 2013; Margolis et al., 2004), a pattern also replicated in our study (women: M = 2.01 [SD = 1.51] vs. men: M = 2.26 [SD = 1.49], t(1435) = -3.15, p = .002, d = .17). Although the exact mechanisms underlying these sex differences are difficult to pinpoint, research has suggested that female sex hormones could potentially delay the development of insulin resistance in women, at least up until menopause (Szmuilowicz, Stuenkel, & Seely, 2009).

Men and women also exhibit considerable differences in lifestyle and health behaviors that could moderate their susceptibility to glucoregulatory decrements. For example, across adulthood, women are more interested in receiving professional advice on disease prevention than men (Deeks, Lombard, Michelmore, & Teede, 2009) and are less likely to engage in risky behaviors such as smoking, alcohol consumption, and unhealthy eating habits (Dawson, Schneider, Fletcher, & Bryden, 2007; Wardle et al., 2004). Considering the importance of lifestyle variables for healthy glucose metabolism (McAuley et al., 2002), it is possible that the downstream consequences of insulin resistance might take longer to develop in women than in men (Clegg, 2012), making men more susceptible to its negative effects on well-being.

Recent studies have suggested that glucose ingestion can support older adults' preference for positive information (Mantantzis et al., 2017) and overall levels of positive affect (Mantantzis et al., 2018). Our findings go one step further to show that individual differences in glucoregulatory capacity are closely related to well-being trajectories in old age. Extending earlier reports of associations between gluco regulatory control and positive affect in older women (Tsenkova et al., 2007), our study is among the first to examine associations between objective indices of glucoregulatory capacity and a range of well-being indices in older men and women. Our findings support the notion of glucoregulatory capacity as a factor contributing to preserved well-being among older men

We note that women in our sample reported higher levels of life satisfaction than men. However, this advantage was found only after adjusting for sociodemographic and health characteristics, suggesting that functional limitations might be particularly detrimental for women's well-being (see also Pinquart & Sörensen, 2001). We also observed interactions between insulin resistance and physical health characteristics, indicating that health variables might moderate associations between insulin resistance and well-being. For example, in line with studies linking greater grip strength with better prognosis in patients with diabetes (Celis-Morales et al., 2017), grip strength in our study seemed to buffer insulin resistance-related decrements in well-being.

Limitations and Outlook

The design of our study did not allow tracking of developmental changes in insulin resistance over time. Whereas estrogens may protect women from systemic conditions (e.g., diabetes), this advantage tends to disappear after menopause, with women eventually reaching similar risk levels as men (Szmuilowicz et al., 2009). It would be informative to examine how insulin resistance changes across late adulthood, whether this differs between men and women, and how such changes are intertwined with changes in well-being. Also, associations between insulin resistance and cognitive outcomes (Kong et al., 2018) and between cognition and well-being (Wilson et al., 2013) are well known. Future research should test whether and how cognitive functioning might be mediating associations between glucose regulation and trajectories of well-being

In addition, we had no hormonal data or information on whether women in our sample had received hormone replacement therapy. This would have been highly informative because hormone replacement therapy improves glycemic control and lowers the risk for developing diabetes (Jelenik & Roden, 2013; Szmuilowicz et al., 2009). It would also be important to examine the role of lifestyle factors (e.g., diet and exercise) in buffering the well-being decrements arising from insulin resistance.

Because our participants were in good health (e.g., low morbidity), our results may not generalize to less healthy older adults. Also, our sample consisted mainly of older adults around the age of 70 years, and we can only speculate about the picture that

² Repeating the analyses after excluding the 49 participants with a history of diabetes but normal glycemic values revealed substantively the same results as reported.

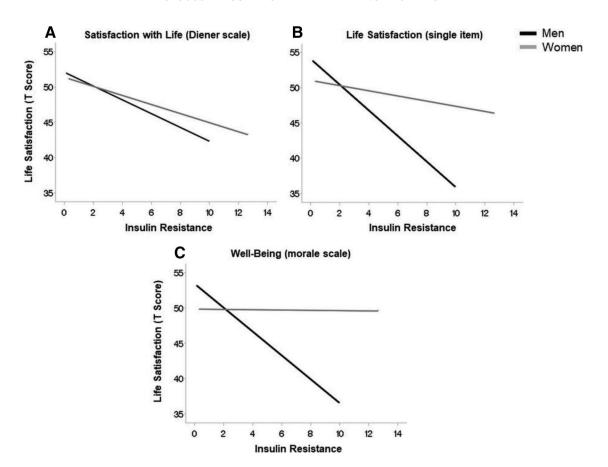


Figure 1. Differences between men and women in how insulin resistance is associated with levels of satisfaction with life (Diener scale, upper left-hand Panel A), life satisfaction (single item, upper right-hand Panel B), and well-being (morale, lower Panel C). It can be obtained that poor glucose regulation (i.e., higher insulin resistance) is associated with lower levels of well-being consistently among men, whereas findings are inconsistent among women, with two of the three well-being measures not evincing an association. These differences between women and men were maintained across old age and were independent of overall morbidity as well as specific performance-based indicators of physical and cognitive functioning.

emerges in very old age (e.g., 80s and 90s). Considering that well-being drops sharply with approaching death (Gerstorf et al., 2016), it would be useful to assess whether individual differences in glucoregulatory capacity can buffer terminal decline in well-being.

Conclusions

The present study examined the role of glucose regulatory capacity in older adults' well-being and cognition. We identified sex-specific associations of poor glucose regulation with well-being trajectories, with insulin resistance predicting lower levels of well-being among older men but not women. This finding could be attributed to female sex hormones protecting women from decrements in glucoregulatory capacity. Further research into how individual differences in physiological mechanisms can shape older adults' well-being (see also Mantantzis, Schlaghecken, & Maylor, 2018) could offer important insights into the process of successful aging.

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