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Psychological well-being and salivary markers of inflammation: The moderating effect of age

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Abstract

Increasing evidence suggests a significant impact of higher psychological well-being (PWB) on health outcomes; however, such associations have been studied exclusively in middle-aged to older adults. This study examined the aging effect on PWB measures as well as the moderating effect of age on the link between PWB and inflammation, using salivary markers by comparing the younger adults ($n = 127$; $M_{age} = 22.98$ years) versus older adults ($n = 75$; $M_{age} = 75.60$ years). Older adults showed significantly lower levels of PWB, particularly regarding purpose in life and personal growth. Moreover, higher purpose in life was associated with lower salivary IL-1ß and IL-6 ($b = 0.83$, $p < .001$; $b = 0.81$, $p < .01$) only in the older adult group but not in younger adults. These findings

highlight the potential buffering effect of the sense of living well on physiological pathways in later life.

KEYWORDS

aging effect, CRP, IL-1ß, IL-6, purpose in life, salivary inflammatory marker

INTRODUCTION

The sense of living a worthwhile life is a critical component of eudaimonic well-being. Eudaimonic well-being is usually indexed by the scale of psychological well-being (PWB) (Ryff & Keyes, 1995), which encompasses a sense of autonomy, personal growth, purpose in life, environmental mastery, and self-acceptance. PWB has been linked to a wide range of physical health outcomes, including favorable immune gene expression profiles (Fredrickson et al., 2013, 2015; Lee et al., 2020), reduced risk of chronic diseases, and increased likelihood of healthy aging (Boehm & Kubzansky, 2012; Ryff, 2017; Steptoe, 2019). In particular, a sense of purpose in life, a key component of PWB, has emerged as a candidate psychological factor that can modify health behaviors and further improve physical health outcomes. For example, having a higher sense of purpose in life is significantly associated with reduced levels of all-cause mortality and cardiovascular events (Alimujiang et al., 2019; Cohen et al., 2016; Kim et al., 2021; Shiba et al., 2021). Moreover, having purpose and meaning in life reduces biological risk profiles such as inflammation and allostatic load (Steptoe & Fancourt, 2019; Zilioli et al., 2015). Interestingly, however, previous research has primarily focused on PWB as reducing age-related functional declines, such as mortality and aging-related diseases, in middle-aged to older adults, and has been less investigated in younger adults. Therefore, whether such associations between PWB and health are still valid in young adults requires more attention.

Inflammatory markers have been widely investigated as links between psychological factors and biological consequences. Peripheral pro-inflammatory markers, such as C-reactive protein (CRP) and IL (interleukin)-6, have been quantified in serum to infer physiological conditions indicating the presence of low-grade inflammation (Baumeister et al., 2016; Muscatell et al., 2018). Such low-grade inflammation in serum has been found across various adverse conditions, including childhood trauma, lower socioeconomic status, and depressive symptoms (Baumeister et al., 2016; Miller & Raison, 2016; Muscatell et al., 2018). Recently, salivary markers have emerged as alternatives to blood sample specimens in the pursuit of timely, cost-effective, and noninvasive methodologies to detect inflammatory markers (Engeland et al., 2019; Yoshizawa et al., 2013). There is increasing interest in validating the salivary markers of inflammation in psychoneuroimmunology research. Recent studies have suggested that measures of salivary inflammation are consistently enhanced by acute psychosocial stress (Sjögren et al., 2006; Slavish et al., 2015; Slavish & Szabo, 2021) as well as chronic stress (Martínez et al., 2018). However, limited studies have examined the impact of psychological protective factors on the salivary markers of inflammation.

The aging process entails continuous mental and physical changes. As conceptualized by the term "inflammaging," people confront physiological changes as they age, including an altered immune system also known as "immunosenescence"(Calder et al., 2017; Franceschi et al., 2000). An altered immune system is typically accompanied by elevated levels of chronic

low inflammation, which may increase the susceptibility to infection linked to higher morbidity and mortality in older adults (Calder et al., 2017; Piber et al., 2019; Puzianowska-Kuźnicka et al., 2016). In a similar way, PWB also changes throughout life. Especially, purpose in life and growth were lower in older adults than in younger and middle aged adults (Mackenzie et al., 2018; Ryff, 1989). A longitudinal analysis also confirmed that personal growth and purpose in life declined with age, whereas other dimensions of PWB (e.g. positive relation with others) showed inconsistent differences (Springer et al., 2011).

The primary objective of this study was to examine differences in PWB, salivary inflammatory outcomes, and the links between the two across different age groups: younger and older adults. Although the link between mental well-being and physiological outcomes has been investigated in middle-aged populations in Western cultures, relatively few studies have been conducted in other cultures and populations. For this, we examined how age (i.e. younger vs. older adults) was associated with (1) PWB and its subscales, (2) salivary inflammatory markers, and (3) if age moderates the association between PWB (and its subscales) and salivary inflammatory markers. In the current study, we selected CRP and IL-6, the two most commonly used markers related to social and behavioral variables (Giudice & Gangestad, 2018) as well as IL-1ß, another pro-inflammatory marker whose reactivity to stress was validated using saliva samples (Szabo et al., 2018; Szabo & Slavish, 2020).

METHODS

Participants

Two different age groups ("younger" vs. "older" adult groups) were recruited to examine the moderative effect of age on well-being measures and inflammatory markers. Participants were recruited from three different sites; the "younger" participants were recruited from two universities (Seoul National University and Sungkyunkwan University) via online announcements with the targeted population aged between 18 and 35 years, and mentally and physically healthy (i.e. absence of chronic diseases) determined by the participants. The "older" participants were recruited through a subpopulation of the Korean Social Life, the Health and Aging Project (KSHAP), a community-based longitudinal cohort study wherein the baseline age of the participants was above 60. Participants diagnosed with neurological disorders or major psychiatric illnesses were excluded via telephone interview. Additionally, participants with periclinal cognitive impairment who scored 1.5 standard deviations (SD) from normative data after adjustments for age, sex, and education on the Mini-Mental State Examination for Dementia Screening (MMSE-DS) were excluded. The mean age of the younger group ($n = 127$) was 23.0 years (SD = 2.9) whereas that of the older group ($n = 75$) was 75.6 years (SD = 5.7). All procedures were reviewed and approved by the Institutional Review Boards of Seoul National University (for the older and younger groups) and Sungkyunkwan University (for the younger group). All participants provided written informed consent after they were briefed on the study procedures.

Collection of salivary samples for analyzing CRP, IL-1ß, and IL-6 levels

Saliva samples were collected using passive drool. The participants were asked not to eat food for 60 min before sample collection. They rinsed their mouths with water for at least 10 min

before sample collection to remove any food residues. Using a Saliva Collection Aid (SCA; Salimetrics, USA) connected to a collection vial, participants were asked to pull saliva into the mouth and then gently fill the saliva into the collection vial to approximately 1 ml. After collection, the samples were immediately stored at −20°C until analysis.

Salivary samples were assayed to quantify the levels of IL-1ß, IL-6, and CRP using immunosorbent assay kits (Salimetrics, USA). A few samples fell into the out-of-range levels, with maximum measurable concentrations of 3000 pg/ml and 1600 pg/ml for IL-1ß and CRP, respectively ($n = 3$, $n = 13$). The minimum measurable concentration of IL-6 was 0.35 pg/ml, and approximately half of the young participants ($n = 66$) were below the lowest detectable level. Considering that in healthy, normal individuals salivary IL-6 ranges commonly fall below the level of detection, the values of half the lower limit of detection (0.0175 pg/ml) were imputed in the individual according to the methods of some previous studies (Ahmadi et al., 2021; Landau et al., 2018). Inter-assay CV % were 1.08–4.27, 1.04–3.71, and 1.99–2.23 for IL-1ß, CRP, and IL-6, respectively.

Measures

Psychological well-being (PWB)

Individuals' psychological well-being was assessed using the 18-item version of Ryff's scales of Psychological Well-Being (Ryff, 1989, 2014). The mean of the total scores was calculated along with the six key components: autonomy (e.g. "I tend to be influenced by people with strong opinion"), environmental mastery(e.g. "The demands of everyday life often get me down"), positive relations with others (e.g. "Maintaining close relationships has been difficult and frustrating for me"), purpose in life (e.g. "Some people wander aimlessly through life, but I am not one of them"), self-acceptance (e.g. "I like most parts of my personality"), and personal growth (e.g. "For me, life has been a continuous process of learning, changing, and growth"). Participants rated their degrees of agreement with the statements using a 5-point Likert scale (1 = *strongly disagree* to 5 = *strongly agree*); ω = .82 for the PWB total score. All the subscales also demonstrated acceptable reliability; purpose in Life (ω = .65); positive relations with others (ω = .68); personal growth (ω = .65); environmental Mastery (ω = .66); self-acceptance (ω = .71); and autonomy (ω = .6).

Demographic, biometric, and behavioral covariates

Covariates included sex, education, body mass index (BMI), health-related behavior, illness symptoms, anti-inflammatory medicine treatment selected from the previous literature, and biological plausibility (OConnor et al., 2009). Demographic factors, including educational level (coded less than 6 years as 0, elementary graduation as 1, middle school graduation as 2, high school as 3, and college and higher as 4) and gender (male as 0 and female as 1) were controlled. Health-related behaviors (currently smoking as 1 and no smoking as 0), alcohol consumption (glass per week), and BMI were also controlled. Possible confounding factors of inflammation such as anti-inflammatory medicine treatment (yes/no), mouth ulcer (yes/no), and recent physical symptoms (i.e. headache and upset stomach) during the past months were also controlled.

Statistical analyses

Descriptive characteristics of the younger and older groups were compared using independent *t*-tests for continuous variables and chi-square tests for categorical variables. For variables that are not normally distributed, we used the independent two-group Mann–Whitney *U* test for nonparametric test for the group differences. The participants were dichotomized into two age groups (younger vs. older adult groups), which were maintained through the statistical analysis. In moderation analysis, due to bimodal distribution of age (i.e. absence of 30s, 40s, and 50s), age was treated as a dichotomizing, rather than continuous moderator. Multiple linear regression was performed to examine the moderating effect of age group on the link between PWB and inflammatory markers. To further investigate the nature of moderation, we conducted a follow-up simple slope analysis to estimate the effect of age groups (younger vs. older) on the association between PWB measures and inflammatory markers.

Due to the skewness, all three inflammatory markers (IL-1ß, IL-6, and CRP) were log-transformed for linear model analysis, relating salivary inflammation to PWB measures. To treat the out-of-range (OOR) immunoassay data, we applied "winsorization," which is an assay OOR treatment technique (Landau et al., 2019); the samples above the maximum detection values for inflammatory markers (for IL-1ß and CRP [$n = 3$, $n = 13$], respectively) were winsorized; that is, the data point was replaced with the highest value. Furthermore, we performed an auxiliary analysis (i.e. list-wise deletion) restricted to 16 individuals whose values were above the maximum detection value—the additional analysis was to determine whether there would still be an association between purpose in life and inflammatory markers in the subpopulation. With the coefficient of determination (R^2) being reduced due to the smaller sample size (.03 and .04 for IL-6 and IL-1ß, respectively), we still found the significant trend in the subsamples.

RESULTS

Characteristics of participants

In total, 202 individuals participated in this study; 75 participants were in the older group (mean age = 75.6, SD = 5.6 years) whereas 127 participants were in the younger group (mean age = 22.98, SD = 2.93 years). The participants in the older group were significantly less educated, had a higher BMI, and took more anti-inflammatory medicine in the last 24 h, as compared with the younger group (Table 1).

Differences in PWB and inflammatory markers between the age groups

Overall, the total PWB score was significantly higher in the younger group than in the older group ($p < .001$; Table 2). However, there were heterogeneities across the subscale scores; participants in the older group reported marginally higher scores in autonomy and environmental mastery but significantly lower scores in personal growth and purpose in life compared with the younger group (Table 2).

In older participants, the levels of CRP, IL-1ß, and IL-6 were significantly higher than those in younger participants (Figure 1): independent *t*-test, $t(130.28) = 2.71$, $p < .001$ for CRP, $t(144.41) = 11.743$, $p < .001$ for IL-1ß, $t(192.23) = 10.37$, $p < .001$ for IL-6, respectively.

TABLE 1 Basic characteristics of the study participants

	Older ($N = 75$)	Younger ($N = 127$)	p-value[a]	Effect size
Age	75.60 (5.65)	22.98 (2.93)	<.001	11.69
Highest level of education			<.001	0.94
Less than 6 years	22 (29.3%)	0 (0.0%)		
Elementary school	32 (42.7%)	0 (0.0%)		
Middle school	13 (17.3%)	0 (0.0%)		
High school	4 (5.3%)	3 (2.4%)		
College/university or higher	4 (5.3%)	124 (97.6%)		
Gender			.095	0.11
Male	34 (45.3%)	73 (57.5%)		
Female	41 (54.7%)	54 (42.5%)		
BMI	24.42 (3.39)	21.95 (2.47)	<.001	0.83
Smoking (yes)	4 (5.3%)	18 (14.2%)	.051	0.12
Alcohol consumption (glasses/week)	0.95 (1.90)	1.35 (1.11)	.057	0.26
Physical symptoms (0–8)	2.48 (1.54)	2.49 (1.86)	.974	0.01
Anti-inflammatory medicine (yes)	8 (10.7%)	0 (0.0%)	<.001	0.24
Mouth ulcer (yes)	3 (4.0%)	3 (2.4%)	.508	0.02

[a]p-values were calculated using the independent sample t-test (Cohen's d for the effect size) for continuous variables or the chi-square test (Cramér's V for the effect size) for categorical variables.

TABLE 2 Psychological well-being scores in older versus younger group

	Older ($N = 75$)	Younger ($N = 127$)	p-value	Effect size
PWB total	3.58 (0.44)	3.77 (0.52)	.003	0.21
Positive relations with others	3.65 (0.86)	3.70 (0.89)	.57	0.04
Self-acceptance	3.71 (0.81)	3.71 (0.68)	.93	0.01
Autonomy	3.53 (0.74)	3.29 (0.83)	.06	0.13
Personal growth	3.50 (0.83)	4.35 (0.60)	<.001	0.51
Environmental mastery	3.75 (0.73)	3.52 (0.76)	.08	0.12
Purpose in life	3.34 (0.78)	4.08 (0.79)	<.001	0.43

Note: The reported values are the mean with standard deviation in the parentheses. p-values and effect sizes indicate the results from independent two-group Mann–Whitney U tests.

Age as a moderator of the link between inflammation and PWB

We examined the moderating effect of the different age groups on the association between inflammatory markers and PWB measures. First, the main effects of age were significant in relation to the levels of IL-1B and IL-6 after controlling for the covariates (e.g. demographic factors, BMI, and smoking/alcohol consumption); $b = -4.07$ [−7.09, −1.04], $p = .01$ and $b = -4.84$ [−8.58, −1.10], $p = .01$, respectively, but the PWB total scores were not related to either of them; $b = -0.45$ [−1.13, 0.22], $p = .19$ and $b = -0.60$ [−1.43, 0.23], $p = .16$, respectively. Neither of age nor PWB total scores were significantly associated with CRP after controlling for the covariates; $b = 1.51$ [−0.77, 3.78], $p = .19$ and $b = 0.28$ [−0.22, 0.79], $p = .27$,

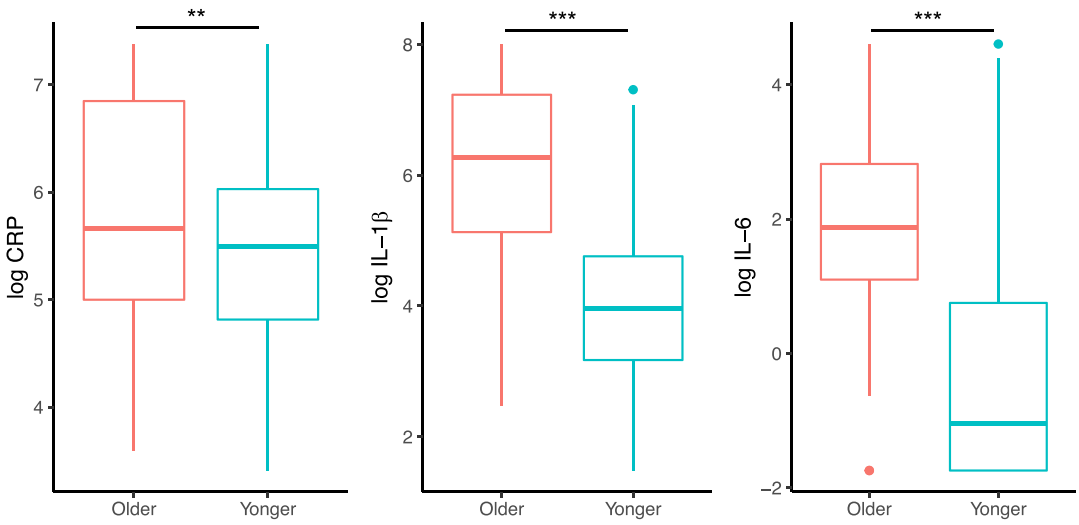

FIGURE 1 Salivary inflammatory markers in the younger versus older group

respectively. The main effects of and each PWB subscales are presented in Table S1. Moreover, we did not find a significant effect of age on the association between the total score of PWB and any of the three inflammatory markers: age group × PWB total score $b = 0.43$ [−0.39, 1.24], $p = .30$ for IL-1ß, $b = 0.53$ [−0.48, 1.53], $p = .30$ for IL-6 and $b = -0.44$ [−1.05, 0.18] for CRP, $p = .16$, respectively.

When we further examined the aging effect on PWB and inflammatory markers among the six subscales, we found a significant moderating effect of the different age groups on the link between purpose in life and inflammatory markers: $b = 0.83$ [0.37, 1.30], $p < .001$ for IL-1ß, $b = 0.81$ [0.23, 1.40], $p < .01$ for IL-6 and $b = 0.06$ [−0.31, 0.43] for CRP, $p = .16$, respectively (Figure 2). The other five PWB measures did not show any interactive effects with any of the inflammatory markers.

Given the moderation of purpose in life by age group, we conducted a follow-up simple slope analysis to estimate separate association coefficients for each age group (Figure 2). In older adults, a higher purpose in life was significantly associated with lower salivary inflammatory markers (for IL-1ß, $b = -0.61$, SE = .19, $p < .01$; for IL-6, $b = -0.61$, SE = .27, $p < .05$), whereas in the younger group, the associations between the two were not significant (for IL-1ß, $b = 0.20$, SE = .14, $p = .14$; for IL-6, $b = 0.29$, SE = .19, $p = .13$).

We performed the same analysis after excluding extreme values ($n = 187$). The moderating effect of age was still significant (for IL-1ß, age × purpose in life, $b = 0.78$ [0.30, 1.25], $p = .001$; for IL-6, age × purpose in life, $b = 0.77$, [0.18, 1.36], $p = .011$). The slope analysis also showed the same patterns (for IL-1ß, $b = -0.57$, SE = .20, $p < .01$; for IL-6, $b = -.051$, SE = .25, $p < .05$), whereas in the younger group, the associations between the two were not significant (for IL-1ß, $b = 0.21$, SE = .14, $p = .13$; for IL-6, $b = 0.26$, SE = .17, $p = .14$).

DISCUSSION

The main aim of this study was to examine the effect of age on the link between PWB and inflammation. Older adults showed significantly higher levels of all salivary markers of

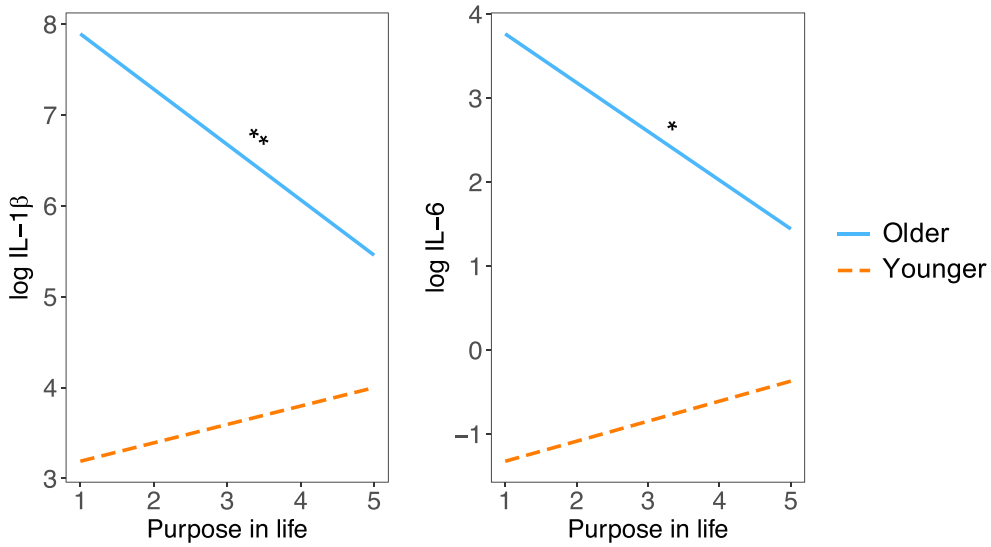

FIGURE 2 The moderative effect of age on the sense of purpose in life and inflammation

inflammation but lower levels of PWB, especially for purpose in life and personal growth. Such heterogeneities were also found in relation to the level of inflammation markers; overall scores of PWB and other subscales did not show any association with inflammation markers but a higher purpose in life was linked to lower salivary inflammatory markers of IL-1ß and IL-6. In that PWB scales converge multidimensional perspectives of eudaimonic well-being and each of the six dimensions represents various perspectives of human thriving (Ryff, 1989, 2014), different subscales may show *related but distinct* characteristics (Ryff et al., 2021). Our findings suggest that a higher purpose in life is linked to lower levels of the salivary inflammatory markers of IL-1ß and IL-6. However, a sense of purpose in life was only beneficial for those over 60 years but not those under 40. Notably, the current study also confirmed the aging effect on levels of PWB outcomes; older adults have significantly lower levels of purpose in life and personal growth but tends to have higher levels of autonomy and environmental mastery. The current findings are well-fitted and consistent with previous findings of the aging effect on PWB measures from a longitudinal design (Springer et al., 2011) as well as cross-sectional analysis (Mackenzie et al., 2018; Ryff, 1989). These findings confirmed that older age is positively associated with indicators of experiencing greater freedom and lesser control from others compared with younger people whereas they get limited opportunities to pursue their goals and continuously grow themselves, conceptualized as *purpose in life*.

Interestingly, although purpose in life was significantly lower in older adults, it exerted protective effects against inflammatory health markers. The current findings are in accordance with previous findings, which suggest that purpose in life serves as a protective buffer against age-related negative conditions; purpose in life alleviates the increased levels of pro-inflammatory markers associated with multiple chronic conditions in older adults (Friedman & Ryff, 2012). Moreover, recent evidence suggests that a higher purpose decreases the risk of age-related conditions such as stroke (Kim et al., 2013), lower allostatic loads (Zilioli et al., 2015), and lower mortality (Alimujiang et al., 2019; Boyle et al., 2009). One of the functional mechanisms between a higher sense of purpose in life and health outcomes is characterized by health

behaviors such as physical activity, fewer sleep problems, fewer chances of addictive behavior, and maintaining a healthy range of BMI (Kim, Ryff, et al., 2020; Kim, Shiba, et al., 2020). Such a link between purpose in life and health behavior may serve as a specific factor to promote health outcomes compared with other PWB subscales. Consistent with these findings, the present study shows that purpose in life is more strongly and inversely associated with pro-inflammatory markers in older adults than in younger adults. Thus, it suggests that life purpose may promote healthy lifestyle practices, which is especially crucial for maintaining physiological and mental health in later life.

Purpose in life, however, does not necessarily benefit the health outcomes of younger adults. As previous research has targeted middle-aged to older adults, the protective role of purpose in life on health is still elusive. Although one recent study suggests that PWB is linked to down-regulated inflammatory gene expression, and this association is stronger in older adults (Lee et al., 2020), the supportive mechanisms for such blunt associations occurring in younger adults are less studied. We may speculate that younger adults with higher purpose or goals in life may face more challenges with heightened life expectations and self-development, which, in turn, may burden their health. The current study suggests that having a purpose in life (or PWB) may differ between older and younger adults, possibly through differential cognitive appraisals and behavioral strategies. Future studies are further needed to delineate the effect of a higher purpose in life on psychological and physiological outcomes especially in younger and middle-aged adults.

There are several limitations to the present study. First, although the current study intended to investigate the aging effect on well-being and health, it would be ideal to control all other socio-environmental conditions at a similar level. However, due to generational differences in education levels and unmeasured cultures, it cannot be ruled out that the moderating effect of age may be influenced by other factors considering that the gap in educational level. Other than the educational level, in South Korea, older adults have encountered the World War, Korean War, and rapid industrialization; thus, they may differ from the younger generation in significant ways. Future studies should attempt to reduce such cohort effect possibly by incorporating younger people with lower educational attainment and by using longitudinal studies within-subjects designs. Second, the cross-sectional design of the current study prevented us from drawing a causal relationship between PWB and inflammatory measures. Future studies are needed to explore life course changes more thoroughly in health markers and well-being measures by tracking the longitudinal changes in the associations between the two. Third, there was heterogeneity in the results with the three selected salivary markers of inflammation; only cytokines (IL-1ß and IL-6) were significantly associated with psychological conditions, whereas the acute phase protein (CRP) was not. Salivary measures of inflammation may show divergent linkages across psychological measures because of differential mechanisms of synthesis and circulation. For example, CRP is secreted from the liver (Marnell et al., 2005), whereas cytokines are produced locally in the mouth and saliva from the salivary glands (Desai, 2014). Since the levels of IL-6 were below the lowest detectable level in approximately half of the young participants, it cannot be ruled out that the restriction of range in the younger adult group may impact on the moderation of age on the link between salivary inflammatory markers and PWB variables. Finally, several studies have revealed correlation measures of IL-6/IL-1ß between saliva and blood serum (Cullen et al., 2015; Fernandez-Botran et al., 2011; Riis et al., 2014) suggesting that salivary markers reflect systemic inflammation. Even though the participants provided the possibility of oral inflammation (e.g. presence of mouth ulcer) and the chance of mouth ulcer was very low (only six out of 202), there is a dearth of information on the quantitative

assessment of oral health by a qualified dentist. As salivary inflammation is primarily influenced by oral health, especially those that are locally produced, future studies with a more comprehensive and objective diagnosis of oral health are needed. Moreover, future studies should also consider the factors that impact the level of inflammatory markers in saliva (e.g. flow rate and the level of total protein in saliva). Future work is needed to elucidate the specific mechanisms involving salivary markers of inflammation in the psychological process to understand how systemic inflammation interacts with human behavior and to draw conclusions from measures of salivary inflammation that pertain to systemic immunity or generalized health.

Despite these limitations, the current study provides evidence for a growing body of research on salivary inflammatory markers related to psychological measures. In particular, this study investigated the impact of positive psychological conditions on salivary biomarkers. The current findings suggest that even though social roles are limited in older adults, when they have higher levels of purpose in life, which, in turn, may manifest more significant health benefits including lower levels of inflammatory markers.

CONFLICT OF INTEREST

We have no known conflict of interest to disclose.

ETHICS STATEMENT

All procedures were reviewed and approved by the Institutional Review Boards of Seoul National University and Sungkyunkwan University.

DATA AVAILABILITY STATEMENT

The data that support the findings of the study are available from the corresponding author upon reasonable request.

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