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Personality pathways to mortality: Interleukin-6 links conscientiousness to mortality risk

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ABSTRACT

Personality is associated consistently with mortality hazards, but the physiological pathways are not yet clear. Immune system dysregulation may be one such pathway due to its role in age-related morbidity and mortality. In this preregistered study, we tested whether interleukin-6 (IL-6) and C-reactive protein (CRP) mediated the associations between personality traits and mortality hazards. The sample included 957 participants (M ± SD = 58.65 ± 11.51 years; range = 35–86 years) from the Midlife in the United States Survey that had 14 years of follow-up. Higher conscientiousness was associated with lower mortality hazards, with each one standard deviation higher conscientiousness associated with a 35% lower mortality risk. IL-6, but not CRP, partially mediated this association, with IL-6 accounting for 18% of this association in the fully adjusted model. While there was initial evidence that the biomarkers mediated both neuroticism and agreeableness and mortality risk, the indirect effects were not significant when controlling for the sociodemographic variables. Taken together, higher conscientiousness may lead to a longer life partially as a result of lower IL-6. This work highlights the importance of biological pathways that link personality to future mortality risk.

1. Introduction

Personality traits, as operationalized by the Five Factor Model (FFM; also referred to as the "Big Five"), have been linked consistently to long-term health outcomes, including mortality (Roberts et al., 2007). Robust evidence indicates that higher conscientiousness – a tendency to be responsible, organized, and capable of self-control – is associated with lower risk of mortality (Graham et al., 2017; Jokela et al., 2013). Low scores of this trait, for example, are associated with an approximately 40% increased risk of mortality over an average of six years of follow-up (Jokela et al., 2013). In contrast, neuroticism – a tendency to experience more negative emotions such as fear and sadness – tends to be associated with elevated mortality risk (Graham et al., 2017), also across long follow-up periods in very old age (O'Súilleabháin and Hughes, 2018). However, protective effects for neuroticism and mortality risk have also been reported (Weiss and Costa, 2005). The evidence has been more mixed for the remaining personality traits within the FFM (e.g. Mroczek and Spiro, 2007; Ferguson and Bibby, 2012; O'Súilleabháin and Hughes, 2018). The consistent evidence that personality, particularly conscientiousness, is associated with mortality has led to great interest in identifying the pathways that explain this association.

Stemming from developmental psychology (Baltes and Goulet, 1970), the lifespan perspective is one that provides considerable avenues to view the possible ways that personality may impact mortality risk across the life course. As discussed by Hampson and Friedman (2008), both the critical period models (whereby exposure to risk during critical periods have longer-lasting effects than at other times) and accumulation models (impact of exposures to risk accumulates across the lifespan) have been well suited to examine personality and health associations. Most work on the possible pathways that contribute to the relation between personality and long-term mortality risk has focused on health-related behaviors (Friedman et al., 1995; Mroczek et al., 2009;

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Turiano et al., 2015, 2012; Graham et al, 2017). Notably absent from this existing literature is the direct examination of underlying physiological mechanisms that may contribute to the predictive effect of personality on mortality risk.

Decades of research have established the importance of the complex structure of the immune system in health processes across the lifespan. Two markers, cytokine interleukin 6 (IL-6) and the acute phase protein C-reactive protein (CRP) are central to the immune system. Both of these biomarkers are historically thought of in the context of inflammation that involves the body's defences in responding to actual or potential infections. However, recent research has highlighted the breadth of processes beyond inflammation that both IL-6 and CRP are related to which are also critically important to health across the lifespan (Del Giudice and Gangestad, 2018). Both of these biomarkers have been regularly implicated as critical to disease-specific and all-cause mortality (Li, H. et al., 2017, Li, Y. et al., 2017; Proctor et al., 2015; Emerging Risk Factors Collaboration, 2010). These biomarkers outperform traditional health risk prediction methods such as the Framingham Risk Score (DeFilippis et al., 2015) and are linked to the onset and development of chronic illnesses (Netea et al., 2017; Vasto et al., 2007).

Over the last decade, the idea that personality traits are associated with both IL-6 and CRP has received growing interest (Sutin et al., 2010; Luchetti et al., 2014). Evidence suggests that conscientiousness may have a protective role in inflammatory-related biomarkers (Luchetti et al., 2014; see also Allen and Laborde, 2017; Sutin et al., 2018; Elliot et al., 2017; Turiano et al., 2013; Wagner et al., 2019). For example, Luchetti and colleagues (2014) found higher conscientiousness to be associated with lower CRP across three large, US samples ($N > 26{,}000$): For each 1SD higher conscientiousness, the risk of exceeding the clinical threshold of CRP ($\geq$3 mg/l) was lowered by 10–15% across the samples. These results were also supported by a *meta*-analysis of published studies on both CRP (7 studies) and IL-6 (6 studies) where conscientiousness was negatively associated with both of the biomarkers (estimated r was −0.05 for CRP and −0.08 for IL-6; Luchetti et al., 2014). In addition to conscientiousness, the *meta*-analysis found a negative correlation between openness and CRP and no significant associations for extraversion or agreeableness (Luchetti et al., 2014). Higher neuroticism has been associated with higher levels of IL-6 (Sutin et al., 2010), but this association did not replicate in the *meta*-analysis (see Luchetti et al., 2014). Later studies have mostly supported the association between conscientiousness and lower inflammation; the findings for the other traits remain mixed (see Allen and Laborde, 2017; Wagner et al., 2019, Hengartner et al., 2016; Israel et al., 2014; Graham et al., 2018).

Much of the literature to date on the mechanisms between personality and mortality has examined behavioural pathways, with little research examining potential physiological pathways. Some literature has also examined the associations between personality and indices of biomarkers, including allostatic load, and have speculated that physiological dysregulation is one pathway that links personality to poor health outcomes (Stephan et al., 2016). The research that has considered the physiological pathways are either theoretical or solely examine the association between personality and specific biomarkers, not whether these biomarkers mediate the relation between personality and mortality. In this preregistered study, we addressed whether circulating levels of biomarkers could be an underlying mechanism through which personality is associated with mortality risk. Specifically, this research investigated if IL-6 and CRP provide a pathway linking personality and mortality risk over a period of 14 years. This study focused on IL-6 and CRP due to their role in age-related morbidity and mortality and their reported associations within the existing literature on personality and biomarkers. It was hypothesised that both biomarkers would mediate associations of both conscientiousness and neuroticism with mortality risks. For extraversion, openness, and agreeableness, we hypothesized that both IL-6 and CRP would not be a pathway linking them to mortality risk.

2. Method

2.1. Preregistration

Preregistration and related documents for this study are available at https://osf.io/263sf. The data used within this study are publicly available through the Inter-University Consortium for Political and Social Research (ICPSR). All analyses were conducted in accordance with the preregistration.

2.2. Participants

Data for this study were from the Midlife in the United States (MIDUS) study that had started in 1995 with 7,108 noninstitutionalized adults between the ages of 25 and 75 years (Brim et al., 2019). The first follow-up (MIDUS 2) was between 2004 and 2006 with 4,963 participants (Ryff et al., 2017). A subset of these participants took part in a biomarker study ($N = 1255$; Ryff et al., 2019). Each participant was invited to attend a clinical research center for a comprehensive examination by trained medical staff that included the collection of biological specimens, a thorough physical exam, and the recording of medical history data (Ryff et al., 2019). Of the available sample with IL-6 and CRP data ($n = 1{,}235$), some participants did not complete the personality assessment (n = 199) or provide medication data (n = 79). As such, the present sample included 957 adults ($M \pm SD = 58.62 \pm 11.50$ years, range: 35 – 86; females, $M \pm SD = 57.87 \pm 11.27$ years, range: 35 – 86; males, $M \pm SD = 59.58 \pm 11.74$ years, range: 36–85). All protocols reported within this study were granted full ethical approval as part of the MIDUS 2 Biomarker Project, in accordance with the Declaration of Helsinki.

An attrition analysis previously reported by Graham and colleagues (2018) found that those who did not complete the biomarker project were higher in neuroticism, lower in openness to experience, less educated, less healthy, and more likely to be white.

Compared to participants deceased during the follow-up, participants who were alive on the final update were younger ($t = -12.43$, $p < 0.001$, 95% CI [−15.52, −11.29]), more likely to be female ($\chi^2 = 10.81$, $p = 0.001$), higher in conscientiousness ($t = 2.99$, $p = 0.003$, 95% CI [0.045, 0.22]), had lower levels of difficulty in completing activities of daily living ($t = -3.20$, $p = 0.002$, 95% CI [−0.36, −0.09]), lower levels of logIL-6 ($t = -6.03$, $p < 0.001$, 95% CI [−0.25, −0.13]), and did not use oral non-steroidal anti-inflammatory medication ($\chi^2 = 13.01$, $p < 0.001$) at baseline (see Table 1).

2.3. Measures

2.3.1. Mortality

Vital status was determined and collated through several methods (National Death Index (NDI), closeout interviews, and during longitudinal sample maintenance), with the most recent update in October 2018. Because only month and year of death were available for each deceased participant, they were assigned the 15th day of the month as their exact date of death (Turiano et al., 2015). There were 111 deaths across the follow-up ($M \pm SD = 137.15 \pm 26.86$ months; range = 6–171); 846 participants were reported as alive on their most recent update. Time was defined as the number of months between the date of the MIDUS 2 Biomarker assessment and date of death.

2.3.2. Personality

Personality traits were assessed using the Midlife Development Inventory (MIDI) Personality Scales (Lachman and Weaver, 1997). Participants indicated the extent to which 26 adjectives described them on a 4-point Likert scale ranging from 1 "*not at all*" to 4 "*a lot*". Items for each personality traits are as follows: Neuroticism (moody, worrying, nervous, calm [reverse]), Extraversion (outgoing, friendly, lively, active, talkative), Openness to Experience (creative, imaginative, intellect,

Table 1
Descriptive statistics of the present baseline sample.

	Deceased (n = 111) Mean (SD)/%	Alive (n = 846) Mean (SD)/%	Complete Sample (n = 957) Mean (SD)/%
IL-6 (*pg/mL*)*	4.23 (4.18)	2.63 (2.57)	2.82 (2.85)
CRP (*ug/mL*)*	3.73 (7.37)	2.63 (3.79)	2.76 (4.37)
Neuroticism	1.95 (0.61)	2.05 (0.63)	2.04 (0.63)
Extraversion	3.11 (0.60)	3.13 (0.57)	3.13 (0.57)
Openness to Experience	2.97 (0.52)	2.96 (0.52)	2.96 (0.52)
Agreeableness	3.41 (0.48)	3.44 (0.50)	3.44 (0.50)
Conscientiousness	3.35 (0.47)	3.49 (0.43)	3.47 (0.44)
Age (*years*)	70.61 (11.44)	57.09 (10.57)	58.65 (11.51)
Sex (*Female*)	41.4%	57.9%	56%
Race (*White*)	96.4%	92.9%	93.3%
Education	7.63 (2.49)	7.78 (2.46)	7.76 (2.46)
Chronic Conditions	1.18 (1.26)	0.99 (1.29)	1.01 (1.29)
ADL	1.41 (0.71)	1.18 (0.49)	1.21 (0.53)
Smoking (*no*)	42.3%	57.7%	55.9%
Corticosteroid Medication (*no*)	82%	87.9%	87.3%
NSAID Oral (*no*)	33.3%	51.5%	49.4%
NSAID Parenteral (*no*)	88.3%	86.6%	86.8%

Note: * = prior to transformation, ADL = activities of daily living, higher values of ADL refer to greater difficulty in performing activities.

curious, broad-minded, sophisticated, adventurous), Conscientiousness (organized, responsible, hardworking, thorough, careless [reverse]), and Agreeableness (helpful, warm, caring, softhearted, sympathetic). McDonald omegas for each personality trait are as follows (McDonald, 1999): Neuroticism ($\omega_t = 0.74$), Extraversion ($\omega_t = 0.79$), Openness to Experience ($\omega_t = 0.77$), Conscientiousness ($\omega_t = 0.73$), Agreeableness ($\omega_t = 0.82$). Cronbach's α levels were all greater than 0.68.

2.3.3. Inflammatory markers

Blood samples were collated at three examination sites (University of California, Los Angeles (UCLA); Georgetown University; University of Wisconsin). Serum IL-6 was measured using a high-sensitivity enzyme-linked immunosorbent assay (ELISA; R & D Systems). High-sensitivity CRP was assessed via plasma with a particle enhanced immunonephelometric assay (BNII nephelometer from Dade Dehring). IL-6 was assayed in the MIDUS Biocore Laboratory (University of Wisconsin, Madison). CRP was assayed at the Laboratory for Clinical Biochemistry Research (University of Vermont). Intra and inter-assay coefficients of variance were in the acceptable range for both inflammatory markers; IL-6 (3.25, 12.31%), and CRP (4.4%, 5.7%). See Ryff and colleagues (2019) for more details about the biomarker assessment.

2.3.4. Confounding variables

The following variables were included as covariates (each measured at the biomarker clinic visit): age; sex (male, female); race (white, other); education (highest level of education "*attained ranging from no schooling or some grade school*" to "*professional degrees such as PhD or MD*"; smoking (ever smoker versus non-smoker); chronic conditions (total number of doctor-diagnosed medical conditions; e.g., hypertension, heart disease, diabetes, cancer, stroke); and activities of daily living (ADL; the extent to which health impacts their ability to perform ten activities (e.g. bathing, dressing) ranging from "*not at all*" to "*a lot*"). Comprehensive information on medication use was also collated as part of the biomarker project. Each participant was required to bring all their medications to the clinic visit in the original containers, such that medication names and dosages were accurately recorded. Information pertaining to medications were then linked to generic names and corresponding drug IDs via linkage to the Lexi-Data database, which were then linked to their therapeutic and pharmacologic class codes. For this study, any form of corticosteroid (encompassing inhalant, nasal, ophthalmic, otic, rectal, systemic, and topical) medications were dummy coded (no, yes). Both oral and parenteral non-steroidal anti-inflammatory medication (NSAID) were also included as further covariates (no, yes).

The full correlation table of all variables is available in the supplementary materials. Each covariate was selected given they have been repeatedly implicated as critically important in the context of the variables under direct examination within this present study (e.g. National Institutes of Health, 2020; Cutler and Lleras-Muney, 2006; O'Súilleabháin et al., 2019, 2020; Levine et al., 1993).

2.4. Analyses

Statistical analyses were conducted using Mplus Version 8 (Muthén and Muthén, 2020). Cox Proportional Hazards Model was used to estimate the risk of death to consider time-to-event including those reported as alive (censored). While allowing for direct and indirect effects on survival time, a structural equation model framework was utilised to estimate mediation in Cox proportional hazards (Asparouhov et al., 2006). All confidence intervals (CI) are reporting 95% thresholds. To statistically test inflammation as an indirect pathway in the predictive effect of personality for mortality hazards, models included IL-6 and CRP simultaneously as mediators. As outlined previously (Turiano et al., 2015), this approach is critical as it allows for the assessment of both mediators together as their combined indirect effect may significantly explain the association between personality and mortality. This approach also incorporates the correlations between indirect effects (Preacher and Hayes, 2008; Turiano et al., 2015).

A base-10 logarithm transformation was performed on both IL-6 and CRP variables to reduce skewed distributions. CRP levels above 10 mg/L may reflect current infection. These observations ($n = 29$) were retained in the present analysis to provide superior estimates of associations (Moriarity et al., 2021), in addition to the retention of outcome variance that is meaningful (O'Connor et al., 2009). Main analyses were conducted both with and without those observations to determine if estimates changed. Results did not differ. Examination of chronic conditions revealed a number of extreme outlier observations ($n = 6$). Winsorizing was employed to limit the number of chronic conditions to 6 which was deemed to represent the closest observation not deemed suspect (Tukey, 1962). To ensure winsorization did not alter estimates significantly, main analyses were conducted with chronic conditions winsorized at both 5 and 7. Results did not differ. To determine if lag in time (defined as the length of time between when the psychometric and biological data were collated; $M \pm SD = 25.94 \pm 14.67$ months; range = 0–61) could be an important confounding factor, analyses were conducted both with and without controlling for it. Results did not differ. As such, and in line with this variable not being formally included within the preregistration of this study, it was not included as a possible confounding variable. Personality traits were standardized for ease of interpretation, such that associations with personality reflected a difference of one standard deviation. Assessment of Schoenfeld residuals for IL-6 revealed a potential violation of the assumption of proportionality. In accordance with the interaction method when a potential violation of the assumption occurs (Allison, 2010), we included an interaction term of IL-6 and months to death as a covariate for IL-6.

Prior to examining mediation, each variable was assessed as a predictor of mortality. Model 1 tested the effects of personality traits collectively for mortality. Model 2 included sociodemographic factors (age, sex, race, education). Model 3 included health-related confounders (smoking, chronic conditions, activity of daily living, corticosteroid medication, oral NSAID, and parenteral NSAID). Model 4 included both IL-6 and CRP. Following these initial models, a series of models then tested whether the biomarkers mediated this pathway. Specifically, Model 5 examined both biomarker mediation pathways for each personality trait on mortality, with mortality, IL-6, and CRP adjusted for the remaining personality traits not under direct examination. Similar to the

first set of analyses, Model 6 adjusted for age, sex, race, and education and Model 7 further adjusted for smoking, chronic conditions, activity of daily living, corticosteroid medication, oral NSAID, and parenteral NSAID.

3. Results

Several baseline variables had a direct effect on mortality (see Table 2). Consistent with previous analyses of earlier follow-up periods in MIDUS (Graham et al., 2017), Conscientiousness was associated lower mortality risk (HR = 0.74; $p = 0.001$; 95% CI, 0.61–0.87), such that each 1 SD increase in conscientiousness was associated with a 35% reduced risk of mortality. This effect was attenuated with the introduction of demographic controls (HR = 0.80; $p = 0.028$; 95% CI, 0.64–0.96) and the health-related factors (HR = 0.81; $p = 0.038$; 95% CI, 0.65–0.97). The association, however, was reduced to non-significance when adjusted for IL-6 and CRP in Model 4 (HR = 0.83; $p = 0.080$; 95% CI, 0.66–1.00). No other personality trait was associated with mortality. In the fully adjusted baseline model, IL-6 was associated with greater mortality risk (HR = 2.99; $p = 0.010$; 95% CI, 0.49 – 5.49). There was no significant association for CRP (HR = 0.91; $p = 0.733$; 95% CI, 0.42 – 1.40). Of the remaining predictors within the fully adjusted baseline model, age (HR = 1.10; $p < 0.001$; 95% CI, 1.08–1.13) and ADLs (HR = 1.33; $p = 0.043$; 95% CI, 0.96–1.70) were associated with greater mortality risk.

Each personality trait was examined for the potential that IL-6 and CRP may mediate between it and mortality because mediation does not require a direct effect from the predictor to outcome variable (Preacher et al., 2007). The combined indirect effects of both biomarkers were a significant indirect pathway between conscientiousness and mortality risk (Table 3). IL-6 emerged as a robust mediator of the association between conscientiousness and mortality in each model: Model 5 ($p = 0.001$), Model 6 ($p = 0.028$), and Model 7 ($p = 0.032$)[1]. These significant mediation results across models accounted for an estimated 23.46%, 18.47%, and 17.65% of the effect of conscientiousness on mortality through IL-6, respectively (see Table 3). No significant indirect effect for CRP was observed. There was some evidence of an indirect pathway from neuroticism and agreeableness to mortality through IL-6 in Model 5, but neither indirect effect remained significant with the sociodemographic adjustments. There was no significant effect for extraversion or openness. See supplementary tables for all mediation results for extraversion, openness, and agreeableness. While it was not included in the preregistration of this manuscript, we also did an exploratory test for an interaction between neuroticism and conscientiousness on its association with IL-6 and mortality. No significant association emerged.

4. Discussion

We found support for our preregistered hypotheses: Both IL-6 and CRP were an indirect path that partially linked conscientiousness to mortality risk. Examination of both IL-6 and CRP revealed that IL-6 was the significant contributor to this mediating effect. As such, higher conscientiousness was found to be associated with a longer life partially as a result of lower IL-6. Contrary to our preregistered hypothesis, we did not find that CRP itself was a significant mediator. Although there was some initial evidence that the biomarkers mediated both neuroticism and agreeableness and mortality, the indirect effects were not significant when controlling for the sociodemographic variables. Finally, as expected, the biomarkers did not mediate either extraversion or openness and mortality risk.

The conscientiousness findings are critically important because they

[1] This fully adjusted significant finding remained virtually unchanged for conscientiousness whether or not the remaining personality traits were adjusted for within the model.

Table 2
Proportional hazards models predicting mortality.

	Model 1 HR, [95% CI], p	Model 2 HR, [95% CI], p	Model 3 HR, [95% CI], p	Model 4 HR, [95% CI], p
Neuroticism	0.843, [0.666, 1.019], 0.109	1.165, [0.921, 1.409], 0.153	1.107, [0.863, 1.351], 0.366	1.133, [0.873, 1.392], 0.287
Extraversion	0.962, [0.733, 1.190], 0.747	0.910, [0.677, 1.144], 0.473	0.922, [0.683, 1.161], 0.539	0.912, [0.675, 1.148], 0.483
Openness to Experience	1.065, [0.816, 1.314], 0.595	1.176, [0.893, 1.458], 0.187	1.217, [0.922, 1.512], 0.112	1.229, [0.929, 1.529], 0.098
Agreeableness	0.997, [0.800, 1.193], 0.973	0.997, [0.772, 1.222], 0.981	0.954, [0.735, 1.172], 0.685	0.964, [0.740, 0.187], 0.754
Conscientiousness	0.739, [0.609, 0.869], 0.001	0.799, [0.638, 0.959], 0.028	0.809, [0.646, 0.971], 0.038	0.833, [0.663, 1.003], 0.080
Age	–	1.112, [1.088, 1.136], <0.001	1.107, [1.082, 1.131], <0.001	1.100, [1.075, 1.126], <0.001
Sex	–	1.512, [0.900, 2.124], 0.045	1.423, [0.831, 2.015], 0.096	1.403, [0.794, 2.013], 0.127
Race	–	0.991, [0.046, 1.937], 0.986	0.917, [0.029, 1.804], 0.860	0.920, [0.011, 1.829], 0.869
Education	–	0.990, [0.911, 1.069], 0.810	0.994, [0.915, 1.072], 0.877	1.008, [0.924, 1.092], 0.850
Chronic Conditions	–	–	0.970, [0.832, 1.108], 0.673	0.964, [0.824, 1.105], 0.627
ADL	–	–	1.404, [1.024, 1.783], 0.014	1.333, [0.963, 1.704], 0.043
Smoking	–	–	1.341, [0.826, 1.857], 0.134	1.343, [0.812, 1.874], 0.144
Corticosteroid Med	–	–	1.367, [0.701, 2.033], 0.208	1.297, [0.658, 1.937], 0.301
Oral NSAID	–	–	1.217, [0.709, 1.725], 0.356	1.306, [0.757, 1.855], 0.213
Parenteral NSAID	–	–	0.871, [0.266, 1.476], 0.697	0.778, [0.209, 1.348], 0.502
IL-6	–	–	–	2.990, [0.489, 5.490], 0.010
CRP	–	–	–	0.910, [0.420, 1.401], 0.733
AIC	1670.022	1524.160	1513.580	1429.542
BIC	1694.315	1567.840	1586.253	1516.729

Note: HR = Hazard Ratio, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion.

Table 3
Mediation models for conscientiousness and neuroticism predicting mortality.

	Conscientiousness		Neuroticism	
	IL-6 Estimate/HR, [95% CI], *p*	CRP Estimate/HR, [95% CI], *p*	IL-6 Estimate/HR, [95% CI], *p*	CRP Estimate/HR, [95% CI], *p*
Model 5				
Indirect effect[1,^]	−0.080, [−0.126, −0.035], 0.001	0.009, [−0.007, 0.026], 0.274	−0.058, [−0.100, −0.015], 0.009	−0.002, [−0.014, 0.011], 0.806
Total effect[2,^]	−0.341, [−0.524, −0.158], <0.001	−0.251, [−0.431, −0.071], 0.006	−0.192, [−0.416, 0.032], 0.092	−0.136, [−0.354, 0.081], 0.220
Full indirect effect[3,^]	−0.071, [−0.111, −0.031], 0.001		−0.059, [−0.098, −0.020], 0.003	
Direct effect[4,*]	0.771, [0.633, 0.908], 0.004		0.874, [0.684, 1.064], 0.225	
AIC	3472.824		3472.824	
BIC	3579.689		3579.689	
Model 6				
Indirect effect[1,^]	−0.041, [−0.078, −0.005], 0.028	0.001, [−0.016, 0.018], 0.939	−0.016, [−0.041, 0.008], 0.193	0.000, [−0.004, 0.004], 0.940
Total effect[2,^]	−0.222, [−0.428, −0.016], 0.034	−0.180, [−0.386, 0.026], 0.086	0.135, [−0.083, 0.353], 0.226	0.151, [−0.066, 0.369], 0.172
Full indirect effect[3,^]	−0.041, [−0.074, −0.008], 0.016		−0.016, [−0.040, 0.008], 0.181	
Direct effect[4,*]	0.835, [0.663, 1.006], 0.084		1.163, [0.910, 1.416], 0.173	
AIC	5962.820		5891.291	
BIC	6156.910		6085.381	
Model 7				
Indirect effect[1,^]	−0.039, [−0.074, −0.003], 0.032	0.003, [−0.013, 0.018], 0.734	−0.028, [−0.060, 0.003], 0.074	0.002, [−0.008, 0.011], 0.751
Total effect[2,^]	−0.221, [−0.427, −0.015], 0.035	−0.180, [−0.385, 0.024], 0.084	0.096, [−0.131, 0.323], 0.407	0.126, [−0.103, 0.355], 0.281
Full indirect effect[3,^]	−0.036, [−0.068, −0.004], 0.028		−0.027, [−0.056, 0.002], 0.069	
Direct effect[4,*]	0.833, [0.663, 1.003], 0.080		1.133, [0.873, 1.392], 0.287	
AIC	5888.771		5815.731	
BIC	6169.708		6096.668	

Note: HR = Hazard Ratio, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion.
Model 5 adjusts for the remaining personality traits not under direct examination.
Model 6 in addition to the previous adjustment, Model 5 adjusts for age, sex, race, education.
Model 7 in addition to confounding variables in Model 5 and 6, adjusts for chronic conditions, ADL, smoking, corticosteroid medication, oral NSAID, and parenteral NSAID.
^ indicates that the estimate is presented.
* indicates that the HR is presented.
[1] Effect of personality on mortality through the indirect inflammation path.
[2] Effect of the indirect inflammation path and direct path of the personality trait on mortality.
[3] Sum of the indirect paths.
[4] Direct effect of the personality trait on mortality.

directly link a biomarker as a pathway from a personality trait to mortality risk. The importance of IL-6 to physical and cognitive health processes across the lifespan is well established. IL-6 is one of the main inflammatory components associated with age-related pathologies (Franceschi and Campisi, 2014), including central nervous system diseases (Erta et al., 2012), cardiovascular disease (Fontes et al., 2015), and also in the allocation of energetic resources and nutrients relevant to adipose tissue (Del Giudice and Gangestad, 2018). Both genetic and epidemiological research point to dysregulation in the immune system as a common pathway involved in the leading causes of deaths. Similarly, conscientiousness has been associated with a large spectrum of health-related behaviours (Graham et al., 2020), age-related pathologies (Terracciano and Sutin, 2019), coping processes (Sesker et al., 2016), and weight trajectories across the lifespan (Sutin et al., 2011). The IL-6 mediated effect of conscientiousness on mortality is likely not just a function of a single or small number of specific health associations but may permeate immunity and associated physiological systems (e.g., nervous, cardiovascular, respiratory, and endocrine systems). Given its link to morbidity and mortality, IL-6 is likely to be a key modulator between conscientiousness and health outcomes.

Importantly, several avenues that link IL-6 to the etiology of disease across the life span have previously been linked to conscientiousness (Furman et al., 2019). For instance, conscientiousness has been linked to a wide array of health-related behaviours (Bogg and Roberts, 2004; Turiano et al., 2015; Sutin et al., 2011; Graham et al., 2018) with beneficial behavioral and clinical markers that are linked with IL-6, such as moderate alcohol use, less unhealthy eating, minimal drug use, and smoking, healthier weight, and more physical activity. Also outlined by Furman and colleagues (2019), IL-6 is known to have a critical role across physiological systems in response to stress. The role of personality within the context of physiological stress processes have been documented, not just as an averaged response to a single stress exposure (Gallagher et al., 2018), but also a pattern of responsivity across time during a stressful experience (O'Súilleabháin et al., 2019a), and changes in stress (O'Súilleabháin et al., 2019b). Research examining conscientiousness and the complexity of stress responsivity is quite limited. Of note, however, is that many of these behavioral, clinical and biological factors are modifiable and thus suggest pathways that can be intervened upon.

Given the role of negative emotionality in health (Lahey, 2009), we hypothesized that these immunity markers may also be a pathway between neuroticism and mortality. However, following full adjustment for possible confounding variables, no significant associations were found for neuroticism. Despite our interest in neuroticism, the null findings are perhaps not surprising given that previous studies have reported mixed evidence of associations between neuroticism and inflammatory markers (Luchetti et al., 2014). In addition, it is also apparent that the associations between neuroticism, health, and mortality are quite nuanced (see Weiss and Deary, 2020; Graham et al., 2020; O'Súilleabháin et al., 2019).

There are theoretical and practical implications of this research. Theoretical models of personality and health have typically focused on behavioral mechanisms (Turiano et al., 2015); this research identified and provided evidence for a biological pathway. Work on personality and mortality suggests that psychological factors may be helpful to identify who is at most risk for premature mortality and why. It will be important in future work to test the usefulness of personality-informed interventions to improve health outcomes, including reducing the risk of premature mortality. Indeed, while the present study had several strengths, such as an extensive follow-up period and a variety of data forms representing known predictors of all-cause mortality. Limitations should also be noted. While this study focused specifically on both IL-6 and CRP, further research is required to examine other potentially relevant pro- and anti- inflammatory cytokines, and importantly, how the present findings may interact with other cytokines, hormones, and other biomarkers as the mediating pathway is likely to be complex. The

present sample is not a nationally representative sample, and as such, these findings require replication across a diverse range of populations. Additionally, while the personality measure available within the present study demonstrates adequate reliability, this study would have benefited from a more comprehensive personality scale that measured underlying personality facets. Facets would provide a more fine-grained examination of personality associations, which may be particularly important in the context of conscientiousness and biological health indices (Sutin et al., 2018). Given number of events is a critical component in terms of statistical power when computing a cox regression, a limitation with the present study design is that <12% of the sample had died. While there are challenges with inferring cause of death due to complexity with comorbidities at the end of life, it may be worthwhile to examine cause-specific mortality within larger samples to determine if specific causes are responsible for the association within the present study.

To conclude, our results indicate that individuals higher in conscientiousness live longer in part because of lower circulating levels of IL-6. These results provide a critical insight into biological mechanisms that link this personality trait to longevity. In doing so, we highlight the importance and need to identify biological pathways that bridge this link from personality to future mortality risk for future work. This study provides a crucial piece to the personality-health puzzle in suggesting that the biomarker IL-6, which is at the core of inflammatory and aging processes, provides a pathway which partly explains why conscientiousness is associated with long-term mortality risk.

Author contributions

P. S. O'Súilleabháin conceptualized this study. P. S. O'Súilleabháin performed the statistical analyses with assistance from N. A. Turiano, and D. Gerstorf. P. S. O'Súilleabháin, N. A. Turiano, D. Gerstorf, A. Terracciano and A. R. Sutin performed data interpretations. P. S. O'Súilleabháin completed the initial draft of the manuscript with contributions from M. Luchetti, S. Gallagher, and A. A. Sesker. All authors provided critical revisions to the manuscript. All authors approved the final version of the manuscript for submission.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2021.01.032.

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