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Psychological distress in older adults: associations with epigenetic markers of ageing, inflammation, and depression, and joint effects on mortality

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ABSTRACT

Background: Psychological distress is associated with adverse health outcomes. We aimed to assess whether the health impacts of psychological distress could be captured by epigenetic markers of ageing, inflammation, and depression, and whether these markers and psychological distress have a synergistic association with mortality in older Australians.

Methods: Blood DNA methylation data for 1146 participants (31 % females, mean age: 69 years) in the Melbourne Collaborative Cohort Study were used to calculate epigenetic markers of ageing (*PCPhenoAge*, *PCGrimAge*, *bAge*, *DunedinPACE*) and inflammation (C-reactive protein [*mCRP*]), and two methylation scores for depression. Psychological distress was assessed by the Kessler scale (K10). Linear regression was used to assess the associations of K10 with epigenetic markers. Cox models were used to assess the multiplicative and additive interactions of K10 and epigenetic markers in their association with all-cause mortality.

Results: We observed positive associations of K10 with epigenetic markers of ageing and inflammation: per standard deviation (SD), 0.05 (95 %CI: 0.00–0.11) for *DunedinPACE* to 0.10 (95 %CI: 0.05–0.16) for *PCPhenoAge*. Associations of epigenetic markers of ageing with mortality were stronger in participants with higher psychological distress. The relative excess risk due to interaction for *DunedinPACE* was 0.82, 95 %CI: 0.14–1.50.

Conclusion: In older Australians, higher psychological distress was associated with older epigenetic age and higher *mCRP*. Participants with higher levels of both psychological distress and epigenetic markers of ageing and *mCRP* had higher mortality risk. These findings highlight links between psychological and biological health, and the potential importance of considering both for disease risk stratification.

1. Introduction

Psychological distress refers to mental suffering, including symptoms of anxiety, depression, stress, trauma, or other psychological challenges (Mazza et al., 2020). It is associated with substantially elevated morbidity and mortality, impaired quality of life, and overall health care burden (Byles et al., 2014; Sambasivam et al., 2019). Prolonged and intense psychological distress can contribute to mental disorders, such as depression and anxiety (Kessler et al., 2005), which are also associated with substantially elevated mortality, in the case of depression, a reduced life expectancy of up to 13 years (Chan et al., 2023).

DNA methylation (DNAm) is an epigenetic mechanism by which a methyl group is transferred to a DNA molecule, mainly occurring at cytosine-guanine (CpG) sites (Moore et al., 2013). It is affected by both genetic and environmental factors and regulates gene expression (Battram et al., 2022). Numerous epigenome-wide studies have been carried out to develop epigenetic markers of ageing (Belsky et al., 2022; Bernabeu et al., 2023; Levine et al., 2018; Lu et al., 2019), biomarkers of health (Gadd et al., 2022), and health conditions including depression (Barbu et al., 2021). Several of these markers, particularly epigenetic markers of ageing, have been found to be powerful indicators of individuals' health profiles or ageing (Horvath and Raj, 2018; Oblak et al., 2021).

A large body of research has reported positive associations between

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mental disorders such as major depressive disorder (MDD) or post-traumatic stress disorder (PTSD) and epigenetic age (Beydoun et al., 2019, 2022; Han et al., 2018; Liu et al., 2022; Protsenko et al., 2021; Wang et al., 2023b; Wolf et al., 2018; Zannas et al., 2023). A case-control study including 1130 Dutch participants (mean age: 41 years), reported that individuals with major depressive disorder experienced an acceleration in their *HorvathAge* of approximately 0.64 'years', compared with no/mild depressive disorder (Han et al., 2018). Another case-control study of 109 participants (mean age: 40 years, $N_{cases} = 49$), reported that individuals with major depressive disorder were two *GrimAge* 'years' older than depression-free controls (Protsenko et al., 2021). Wang et al. (2023b) used cross-sectional data from 3793 participants from the Health and Retirement Study (HRS) and reported that those with more severe depressive symptoms had 0.4 years higher *GrimAge* compared to those with few/no depressive symptoms. One study reported no association between psychological stress and epigenetic age (Vetter et al., 2022). Additionally, psychological distress is a well-established cause of elevation of inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) (Lawn et al., 2022; Linkas et al., 2022).

Many studies used relatively small sample sizes (Beydoun et al., 2019; Liu et al., 2022; Protsenko et al., 2021; Zannas et al., 2023) or young populations (Beydoun et al., 2019; Han et al., 2018; Zannas et al., 2023), with limited emphasis on global psychological symptoms in the general population such as psychological distress. In addition, epigenetic age algorithms have been greatly improved in recent years, with principal-component (PC)-based measures that are more reliable (Higgins-Chen et al., 2022), and the integration of *GrimAge* components with methylation-based markers of plasma proteins (Bernabeu et al., 2023). Epigenome-wide association studies have also revealed methylation sites associated with MDD, and two epigenetic markers of MDD have been developed and showed some ability in distinguishing depressive individuals from healthy individuals in the original paper (Barbu et al., 2021). These more recent markers have not yet been widely explored, particularly their associations with psychological factors.

In a previous study, we found that epigenetic age was more strongly associated with mortality risk in those who reported 'fair/poor' health than in those who reported 'excellent' health (Li et al., 2024). Self-rated health (SRH) is a subjective health indicator that comprises both physiological and psychosocial aspects of health (Jylhä, 2009).

In the current study, we hypothesised that psychological distress, a subjective indicator of mental health that has been found to be associated with higher risks of mortality and morbidity (Hockey et al., 2022), might also interact with epigenetic markers of ageing, inflammation, and depression in its association with mortality. Therefore, we aimed to assess in a large sample of older Australians: 1) the association between psychological distress and epigenetic markers of ageing, inflammation, and depression; and 2) the potential interaction between psychological distress and these epigenetic markers in their associations with mortality.

2. Methods

2.1. Study sample

We used data from the Melbourne Collaborative Cohort Study (MCCS), a prospective study that recruited 41,513 middle-aged and older Australians (99 % aged between 40 and 69 years, 59 % females) of white European origin between 1990 and 1994 (baseline) (Milne et al., 2017). During 2003–2007, a face-to-face follow-up was carried out. At both waves, socio-demographic, lifestyle, and health data, as well as physical measurements and blood samples were collected.

This study used follow-up data from a subset of 1251 controls from seven nested cancer case-control studies (Dugué et al., 2020, 2021; Geurts et al., 2018; Li et al., 2024). Peripheral blood samples were collected and stored as dried blood spots on Guthrie cards (89 %) or buffy coats (11 %). Genome-wide DNA methylation was measured using the Illumina HumanMethylation450 BeadChip array, and all samples went through the same normalisation and quality control procedures (Dugué et al., 2016; Joo et al., 2013; Milne et al., 2017). Additional details about the variables used in this study can be found in the Supplementary Methods.

Participants were passively followed from the time they attended follow-up interview to 31st December 2019. Deaths were identified by annual record linkage to the Victorian Registry of Births, Deaths and Marriages (Milne et al., 2017).

The MCCS was approved by the Human Research Ethics Committee of the Cancer Council Victoria, Melbourne, VIC, Australia, and informed consent was provided by all participants according to the Declaration of Helsinki.

2.2. Psychological distress

Psychological distress was assessed at the follow-up visit (2003–2007) using the Kessler Psychological Distress Scale (K10) Questionnaire. The K10 scale consists of 10 questions about frequency of symptoms of anxiety (4 items) and depression (6 items) experienced in the past 4 weeks, with a score of 1–5 assigned to each item: 1 = "None of the time" and 5 = "All of the time". Each item has equal weight, with a total score theoretically ranging between 10 (no distress) and 50 (Kessler et al., 2002). The score was log-transformed and standardised to z-score in all analyses. We also considered the thresholds used by the Australian Bureau of Statistics to categorise K10: low: 10–15, moderate: 16–21, and high: 22–50 (Andrews and Slade, 2001).

2.3. Epigenetic markers

We considered four epigenetic ageing measures (*PCPhenoAge*, *PCGrimAge*, *bAge*, and *DunedinPACE*), one epigenetic marker of CRP (*mCRP*), and two methylation risk scores (MRS) of MDD (*MRS* and MRS based on non-smokers [*MRSns*]).

PhenoAge was developed to reflect phenotypic age based on ten clinical markers (Levine et al., 2018). *GrimAge* consists of methylation-based markers of smoking pack-years and seven plasma proteins and predicts mortality (Lu et al., 2019). These measures were trained on principal components (PCs) to improve their reliability, resulting in *PCPhenoAge* and *PCGrimAge* (Higgins-Chen et al., 2022). *bAge* incorporated 6/8 methylation markers from *GrimAge* and 28 protein *EpiScores* (including *mCRP*) (Bernabeu et al., 2023). *DunedinPACE* was developed based on methylation markers of the trajectory of 19 clinical markers over 20 years to estimate the rate of ageing (Belsky et al., 2022). CRP is an inflammatory marker that has been consistently found to be associated with risks of morbidity and mortality (Collaboration, 2010). The *mCRP* score used in this study is one of the protein *EpiScores* developed based on 100 CpGs, and is also included in *bAge* (Bernabeu et al., 2023; Gadd et al., 2022). Epigenetic ageing measures and *mCRP* were calculated using the *methscore* function in R (Xu et al., 2024); *bAge* was calculated based on *PCGrimAge*. The residuals from regression of these markers on chronological age were used as age-adjusted measures.

MRS was developed to predict major depressive disorder based on 196 CpGs, while *MRSns* incorporated 144 CpGs and was trained on a sub-cohort that only included non-smokers who were also in the training cohort of *MRS* (Barbu et al., 2021). Both scores were calculated using weights provided in the original paper (Barbu et al., 2021).

All markers were further standardised to z-scores in all analyses.

2.4. Data preparation

After excluding duplicates (n = 9), participants whose sample failed quality control (n = 12), and participants with missing data in the K10

score (n = 84), the study sample included 1146 participants. A small proportion of missing data in some covariates (0.2–11.9 %, Supplementary Table 1) were imputed using the *missForest* method which performs well with mixed data types and 0–30 % missing data (Penone et al., 2014; Stekhoven and Buhlmann, 2012).

2.5. Statistical analysis

Linear regression models were applied to assess the cross-sectional associations between K10 and the epigenetic markers, where K10 was modeled both as a continuous variable (logK10) and as a categorical variable with low psychological distress (K10 < 16) as the reference level. Three models were considered: Model 1 adjusted for age, sex, and country of birth; Model 2 additionally adjusted for socioeconomic status (measured by the socioeconomic indexes for areas, decile, Supplementary Methods), education level (1–8), smoking status (current, former, never smokers), smoking pack-years (log-transformed), alcohol consumption (grams/day), physical activity (the Metabolic Equivalent of Task hours/week), body mass index (kg/m^2), and diet quality (Alternative Healthy Eating Index, 2010; Chiuve et al., 2012)); Model 3 additionally adjusted for SRH (excellent, very good, good, fair/poor). A restricted cubic spline term (3 knots at the 10th, 50th, and 90th percentiles) was applied to alcohol consumption to account for its non-linear association with various health outcomes (Visontay et al., 2022).

Cox proportional hazard models were used to assess the association between K10 and all-cause mortality. We tested multiplicative interaction on mortality between epigenetic markers and K10 using likelihood ratio tests (LRT). We also explored additive interactions using the method of Knol et al. (2007) to calculate the relative excess risk due to interaction (RERI), where the RERI represents the increase in mortality risk due to the additive interaction that correspond to one SD higher values of both K10 and epigenetic markers. To calculate the 95 % confidence intervals (CIs), we resampled the dataset using the bootstrap method with 10,000 iterations, and extracted the bias-adjusted 2.5th and 97.5th percentiles of the RERI to account for potential bias due to overfitting caused by the bootstrap procedure (Knol et al., 2007). The RERI for categorical variables was also calculated using the method of Li et al. (Li and Chambless, 2007), using dichotomised K10 and epigenetic marker variables. For K10, we grouped moderate (K10: 16–21) and high (K10: 22–50) levels into one category with low psychological distress (K10 < 16) as the reference category, and age-adjusted epigenetic ageing markers were grouped as 'decelerated': <0 or 'accelerated': ≥0, and at median value for *mCRP*, *MRS*, and *MRSns* (0 = low: <median; 1 = high: ≥median).

2.5.1. Sensitivity analysis

We divided the K10 score into its anxiety (4 items, range 4–20) and depression (6 items, range 6–30) subscales, and log-transformed and standardised to z-scores. The same three linear regression models as in the main analyses were used to assess cross-sectional associations with epigenetic markers for the anxiety and depression subscales.

Analyses were conducted with R 4.4.1.

3. Results

3.1. Sample characteristics

The mean age of the 1146 participants was 69 years, and 381 (33 %) died during follow-up, Table 1. The majority of participants (69 %) were male. The median K10 score was 13 points, with 862 (75 %) participants in the low psychological distress category and 8 % of participants had high/very high levels of psychological distress, Supplementary Table 2.

Table 1
Characteristics of the Melbourne Collaborative Cohort Study participants included in the subsample (N = 1146, wave 2: 2003–2007).

Variables	Overall N = 1146	Alive N = 765	Dead N = 381
Age, mean (SD)	69.0 (8.0)	66.5 (7.7)	74.0 (6.0)
Sex, N (%)			
Male	791 (69.0 %)	508 (66.4 %)	283 (74.3 %)
Female	355 (31.0 %)	257 (33.6 %)	98 (25.7 %)
Country of birth, N (%)			
Australia/New Zealand	873 (76.2 %)	574 (75.0 %)	299 (78.5 %)
Northern Europe	101 (8.8 %)	69 (9.0 %)	32 (8.4 %)
Southern Europe	172 (15.0 %)	122 (15.9 %)	50 (13.1 %)
SEIFA score, median (IQR)	6.7 (4, 9)	7 (4, 9)	6 (4, 9)
Education level, median (IQR)	5 (4, 8)	5 (4, 8)	4 (4, 6)
Smoking status, N (%)			
Current smoker	61 (5.3 %)	41 (5.4 %)	20 (5.2 %)
Former smoker	480 (41.9 %)	290 (37.9 %)	190 (49.9 %)
Never smoker	605 (52.8 %)	434 (56.7 %)	171 (44.9 %)
Smoking packyears, mean (SD)	2.85 (2.91)	2.54 (2.84)	3.46 (2.98)
Alcohol consumption, median (IQR)	9.5 (0.4, 22.9)	10.2 (1.1, 23.2)	7.6 (0, 22.5)
BMI (kg/m2), mean (SD)	27.1 (4.3)	27.3 (4.3)	26.7 (4.10)
AHEI-2010, mean (SD)	52.6 (10.0)	53.0 (10.0)	51.7 (10.1)
MET score, median (IQR)	18.2 (7.8, 34.4)	18.9 (8.3, 34.7)	17.3 (7.4, 32.5)
K10 score, median (IQR)	13.0 (11.0, 15.0)	13.0 (11.0, 15.0)	13.0 (11.0, 16.0)
K10 category, N (%)			
A (Low)	862 (75.2 %)	583 (76.2 %)	279 (73.2 %)
B (Moderate)	195 (17.0 %)	132 (17.3 %)	63 (16.5 %)
C (High)	89 (7.8 %)	50 (6.5 %)	39 (10.2 %)
***PCPhenoAge*, mean (SD)**	0.52 (5.85)	0.08 (4.97)	1.39 (7.22)
***PCGrimAge*, mean (SD)**	0.16 (3.37)	−0.24 (3.09)	0.96 (3.76)
***bAge*, mean (SD)**	0.02 (0.44)	−0.03 (0.40)	0.12 (0.50)
***DunedinPACE*, mean (SD)**	0.004 (0.12)	−0.01 (0.11)	0.03 (0.13)
***MRS* for depression, mean (SD)**	−16.3 (2.5)	−16.4 (2.4)	−16.3 (2.6)
***MRSns* (developed in non-smokers), mean (SD)**	−30.4 (9.9)	−30.7 (9.6)	−29.8 (10.5)
***mCRP*, mean (SD)**	−0.12 (0.01)	−0.12 (0.01)	−0.12 (0.01)

*IQR = interquartile range; SD = standard deviation; SEIFA = socioeconomic index for areas; BMI = body mass index; AHEI-2010 = Alternative Healthy Eating Index 2010; MET = Metabolic Equivalent of Task; MRS = methylation risk score.
**All epigenetic ageing measures were age-adjusted.

3.2. K10 and epigenetic markers

Higher levels of psychological distress were associated with higher levels of epigenetic age and *mCRP*. In Model 1, one SD higher logK10 was associated with 0.09-SD (*DunedinPACE*, 95 %CI: 0.04, 0.15, Table 2) to 0.14-SD (*bAge*, 95 %CI: 0.09, 0.20) higher epigenetic age and *mCRP*. After adjusting for socio-demographic and lifestyle-related factors, the association was attenuated: e.g. *DunedinPACE*: β = 0.05, 95 %CI: 0.00, 0.11; *bAge*: β=0.09, 95 %CI: 0.05, 0.14. Compared to low psychological distress (K10 < 16), a moderate level of psychological distress (K10: 16–22) was associated with higher epigenetic ageing and *mCRP* (e.g. per SD, *bAge*, β=0.12, 95 %CI: 0.00, 0.24), and high psychological distress level was associated with even higher levels of these markers (e.g. *bAge*: β=0.34, 95 %CI: 0.17, 0.51). The associations attenuated after further adjusting for SRH. No association was found between K10 and the two epigenetic markers of depression (Table 2).

Table 2
The cross-sectional association between K10 score and epigenetic markers of ageing, CRP, and depression (N = 1146).

				PCPhenoAge			*PCGrimAge*			*bAge*			*DunedinPACE*		
			N	β	95 % CI	P	β	95 % CI	P	β	95 % CI	P	β	95 % CI	P
Model 1[a]	logK10		1146	0.12	0.06, 0.18	4×10^{-5}	0.13	0.08, 0.19	8×10^{-7}	0.14	0.09, 0.20	2×10^{-7}	0.09	0.04, 0.15	0.001
	K10 category[d]	Low	862	Ref											
		Moderate	195	0.18	0.03, 0.34	0.02	0.20	0.06, 0.34	0.01	0.25	0.11, 0.39	7×10^{-4}	0.13	−0.02, 0.28	0.09
		High	89	0.37	0.16, 0.59	7×10^{-4}	0.48	0.29, 0.68	2×10^{-6}	0.49	0.29, 0.69	2×10^{-6}	0.45	0.23, 0.66	4×10^{-5}
Model 2[b]	logK10		1146	0.10	0.04, 0.16	5×10^{-4}	0.08	0.04, 0.13	3×10^{-4}	0.09	0.05, 0.14	8×10^{-5}	0.05	0.00, 0.11	0.04
	K10 category	Low	862	Ref											
		Moderate	195	0.13	−0.02, 0.29	0.08	0.08	−0.04, 0.20	0.19	0.12	0.00, 0.24	0.05	0.03	−0.11, 0.17	0.66
		High	89	0.32	0.11, 0.53	0.003	0.34	0.17, 0.50	8×10^{-5}	0.34	0.17, 0.51	7×10^{-5}	0.34	0.14, 0.53	8×10^{-4}
Model 3[c]	logK10		1146	0.07	0.01, 0.13	0.03	0.06	0.01, 0.11	0.02	0.06	0.01, 0.10	0.02	0.01	−0.05, 0.06	0.78
	K10 category	Low	862	Ref											
		Moderate	195	0.09	−0.06, 0.24	0.24	0.05	−0.07, 0.17	0.41	0.08	−0.04, 0.20	0.19	−0.02	−0.16, 0.13	0.82
		High	89	0.20	−0.02, 0.42	0.07	0.25	0.08, 0.43	0.004	0.23	0.06, 0.41	0.01	0.20	−0.00, 0.41	0.05
				mCRP			*MRS*			*MRSns*					
Model 1	logK10		1146	0.10	0.05, 0.16	2×10^{-4}	0.01	−0.05, 0.07	0.70	0.02	−0.04, 0.08	0.57			
	K10 category	Low	862	Ref											
		Moderate	195	0.14	−0.01, 0.28	0.06	0.10	−0.06, 0.26	0.21	0.05	−0.11, 0.20	0.56			
		High	89	0.35	0.15, 0.55	8×10^{-4}	−0.11	−0.33, 0.11	0.34	0.11	−0.11, 0.33	0.33			
Model 2	logK10		1146	0.08	0.02, 0.13	0.005	0.01	−0.05, 0.07	0.83	0.01	−0.05, 0.07	0.64			
	K10 category	Low	862	Ref											
		Moderate	195	0.07	−0.07, 0.21	0.31	0.09	−0.07, 0.25	0.25	0.04	−0.12, 0.20	0.62			
		High	89	0.27	0.08, 0.47	0.007	−0.13	−0.36, 0.09	0.24	0.11	−0.11, 0.33	0.32			
Model 3	logK10		1146	0.03	−0.02, 0.09	0.25	0.01	−0.06, 0.07	0.86	0.00	−0.07, 0.06	0.92			
	K10 category	Low	862	Ref											
		Moderate	195	0.02	−0.12, 0.17	0.73	0.09	−0.07, 0.25	0.28	0.02	−0.14, 0.18	0.77			
		High	89	0.13	−0.07, 0.34	0.20	−0.15	−0.38, 0.09	0.21	0.07	−0.17, 0.30	0.58			

Epigenetic ageing measures were adjusted for age. All epigenetic markers and logK10 were standardised to a mean of 0 and standard deviation of 1.
[a] Model 1 adjusted for age, sex, and country of birth.
[b] Model 2 additionally adjusted for SEIFA-10, education level, smoking status, smoking packyears, alcohol consumption, physical activity, BMI, and AHEI-2010.
[c] Model 3 additionally adjusted for self-rated health.
[d] The K10 category was defined as: Low: K10 < 16; Moderate: 15<K10 < 22; High: K10 > 21.

3.2.1. *Sensitivity analysis*

The anxiety and depression subscales showed similar associations with epigenetic markers as the full K10 score, with marginally smaller effect sizes for the anxiety subscale, e.g. Model 2, anxiety/*bAge*: β = 0.07, 95 %CI: 0.02–0.12; depression/*bAge*: β = 0.09, 95 %CI: 0.04–0.14, Supplementary Table 3.

3.3. *K10, epigenetic markers and mortality*

A SD higher logK10 was associated with 1.20 (95 %CI: 1.08, 1.32) higher risk of death. Compared with low psychological distress, high psychological distress was associated with more than twice the rate of death (HR = 2.11, 95 %CI: 1.50, 2.98, Table 3), while the hazard ratio was lower for moderate psychological distress (HR = 1.18, 95 %CI: 0.89, 1.55). The association attenuated after adjusting for SRH and lifestyle factors.

For all epigenetic markers of ageing and *mCRP*, the associations with mortality were greater in the moderate and high psychological distress categories than in participants with low distress, Table 3. There was evidence of multiplicative interaction for *DunedinPACE* (P = 0.04), with HR point estimates of 1.27, 1.65, and 1.61 in participants with low, moderate, and high distress, respectively, and for *mCRP* (P = 0.03) with point estimates of 1.27, 1.41, and 2.96, respectively. There was evidence of positive additive interaction of K10 with three epigenetic ageing markers and *mCRP* (Table 3, Supplementary Fig. 1), with RERIs per SD of log(K10) and epigenetic markers ranging between 0.16 and 0.20. As an illustration, compared to participants with low K10 and decelerated *DunedinPACE*, those with high K10 and accelerated *DunedinPACE* had 2.2-fold (95 %CI: 1.6, 2.9) higher risk of mortality, with an RERI of 0.82 (95 %CI: 0.16, 1.48), Supplementary Fig. 1. Adjusting for lifestyle factors and SRH had minimal influence on the interactions between K10 score and epigenetic markers.

Table 3
The association between K10 and mortality, and subgroup analyses of epigenetic age and mortality by K10 categories (N = 1146, N_{deaths} = 376).

Models	Epigenetic markers	Psychological distress levels (K10 categories[a])									Additive interaction[c]		
		Low N = 862, N_{death} = 274			Moderate N = 195, N_{death} = 63			High N = 89, N_{death} = 39			Multiplicative interaction			
		HR	95 % CI	P	HR	95 % CI	P	HR	95 % CI	P	P-int[b]	RERI	95 % CI	P
Model 1[d]	–	Ref.			1.18	0.89-1.55	0.24	2.11	1.50-2.98	2×10^{-5}	–	–		
	PCPhenoAge	1.17	1.06-1.31	0.003	1.33	1.04-1.68	0.02	1.45	1.03-2.04	0.03	0.19	0.15	−0.02, 0.31	0.08
	PCGrimAge	1.41	1.24-1.61	2×10^{-7}	1.60	1.23-2.08	4×10^{-4}	1.99	1.29-3.06	0.002	0.21	0.20	0.03, 0.36	0.02
	bAge	1.38	1.22-1.57	5×10^{-7}	1.66	1.29-2.14	1×10^{-4}	1.73	1.18-2.54	0.005	0.13	0.17	0.02, 0.32	0.03
	DunedinPACE	1.27	1.12-1.43	9×10^{-5}	1.65	1.28-2.13	9×10^{-5}	1.61	1.13-2.30	0.009	0.04	0.16	−0.00, 0.32	0.05
	mCRP	1.27	1.13-1.43	8×10^{-5}	1.41	1.08-1.83	0.01	2.96	1.73-5.06	8×10^{-5}	0.03	0.17	0.01, 0.34	0.05
	MRS	1.06	0.94-1.20	0.31	0.90	0.68-1.18	0.43	0.76	0.51-1.16	0.20	0.27	−0.11	−0.23, 0.04	0.12
	MRSns	0.98	0.88-1.09	0.75	1.06	0.82-1.36	0.66	0.73	0.53-1.02	0.07	0.21	−0.04	−0.13, 0.04	0.34
Model 2[e]	–	Ref.			1.04	0.79-1.38	0.77	1.70	1.17-2.46	0.005	–	–		
	PCPhenoAge	1.14	1.02-1.28	0.02	1.29	1.00–1.67	0.05	1.45	0.95-2.22	0.09	0.06	0.005	−0.02, 0.04	0.75
	PCGrimAge	1.32	1.14-1.54	3×10^{-4}	1.43	1.05-1.95	0.02	2.41	1.09-5.35	0.03	0.05	0.02	−0.03,0.08	0.52
	bAge	1.31	1.12-1.52	6×10^{-4}	1.49	1.10-2.02	0.01	2.41	1.14-5.10	0.02	0.07	0.02	−0.02, 0.08	0.50
	DunedinPACE	1.21	1.06-1.38	0.004	1.64	1.23-2.19	8×10^{-4}	1.48	0.92-2.37	0.11	0.04	0.01	−0.02, 0.07	0.54
	mCRP	1.21	1.06-1.37	0.003	1.30	0.99-1.72	0.06	3.35	1.76-6.36	2×10^{-4}	0.06	0.01	−0.03, 0.06	0.64
	MRS	1.06	0.94-1.20	0.32	0.76	0.56-1.03	0.08	0.77	0.46-1.28	0.31	0.02	−0.01	−0.03, 0.01	0.31
	MRSns	0.96	0.86-1.08	0.51	1.12	0.86-1.44	0.40	0.75	0.51-1.09	0.13	0.10	−0.01	−0.03, 0.00	0.17

*All epigenetic ageing measures were adjusted for age. All epigenetic markers and logK10 were standardised to a mean of 0 and standard deviation of 1.
[a] P-int stands for the p-value calculated from likelihood ratio tests assessing multiplicative interactions.
[b] The K10 category was defined as: Low: K10 < 16; Moderate: 15<K10 < 22; High: K10 > 21.
[c] The additive interaction was quantified using the Relative Excess Risk due to Interaction (RERI) calculated using the method proposed by Knol et al. (2007), and can be interpreted as the amount of increase in the mortality risk that is due to the additive interaction for every one standard deviation increase in logK10 and one standard deviation increase of epigenetic markers. The 95 % CIs were the bias-adjusted 2.5th and 97.5th percentiles of the RERI resampled using bootstrap method with 10,000 iterations.
[d] Model 1 adjusted for age, sex, and country of birth.
[e] Model 2 additionally adjusted for SEIFA-10, education level, smoking status, smoking packyears, alcohol consumption, physical activity, BMI, AHEI-2010, and self-rated health.

4. Discussion

This study found that higher levels of psychological distress in the older population were associated with older epigenetic age and *mCRP* and higher mortality risks. The associations remained positive, reduced by approximately one third, after accounting for SRH as a proxy for overall health status and did not show substantial difference between the anxiety and depression subscales. Epigenetic age and *mCRP* also showed stronger associations with mortality risk in participants with moderate and high psychological distress than in those with low psychological distress. We quantified additive interactions of K10 with epigenetic markers, highlighting the need for considering both psychological and epigenetic factors when stratifying mortality risk.

Although effect sizes are difficult to compare across studies, the associations in previous studies focusing on clinical depression (Beydoun et al., 2022; Protsenko et al., 2021; Wang et al., 2023b) appeared quite strong, and these were close to null in a previous study examining psychological stress (Vetter et al., 2022). Beydoun et al. used 2806 participants from the HRS and reported positive associations for the trajectory of depressive symptom scores over six years with *PhenoAge* and *GrimAge*, and as in our study the association was partly explained by lifestyle and socio-demographic factors (Beydoun et al., 2022). Wang et al. used 3793 participants from the HRS and found that those with high depressive symptoms were 0.4-'year' older in terms of *GrimAge* (Wang et al., 2023b). Wolf et al. synthesised results from four studies (N_{total} = 1251) and reported that lifetime PTSD severity was weakly associated with older *HannumAge* (Wolf et al., 2018). In a small sample of 49 depression cases and 60 healthy controls aged between 20 and 68 years, the cases had much older *GrimAge* (by a median of 2 years) than the controls (Protsenko et al., 2021). A few small studies also reported no association between depressive symptoms or PTSD and epigenetic age (Beydoun et al., 2019; Wolf et al., 2019), although their null results were likely due to small sample sizes, and the use of first-generation clocks which were developed to predict chronological age rather than biological age. Vetter et al. examined the associations between a psychological stress score and epigenetic age in nearly 1000 participants and found a weak association for *PhenoAge* which attenuated to null after adjusting for lifestyle-related and genetic factors (Vetter et al., 2022). In comparison, our study found that e.g. *PCGrimAge* was increased by 0.34 SD in participants with high vs low psychological

distress, which corresponds to a greater effect size of ~1.1 epigenetic age 'years'.

Our results on the association between psychological distress and mortality were similar to previous studies. Hockey et al. reported a 1.6-fold higher mortality risk for people with highly symptomatic psychological distress compared to those with asymptomatic psychological distress in a large cohort over 6-year follow-up (Hockey et al., 2022). Russ et al. synthesised data from 10 cohorts and found similarly elevated mortality risk in participants with higher psychological distress (Russ et al., 2012).

In a previous study using the MCCS data, we observed strong multiplicative interactions between epigenetic age and SRH, where epigenetic age showed strong associations with mortality risk in those who reported 'fair/poor' health, but the association was weak or null in those with 'excellent' self-rated health (Li et al., 2024). Initially, we hypothesised a similar interaction might be found between psychological distress and epigenetic age, since psychological factors were also considered as robust hallmarks of ageing (Faria et al., 2024). However, only weak evidence was found for multiplicative interactions between K10 and the epigenetic markers. Although the associations for epigenetic markers and mortality in the high psychological groups appeared somewhat greater after adjusting for lifestyle and SRH, this might have been due to the lower precision of the estimates rather than a true increase. In addition, SRH, which as a construct also contains psychological aspects of health, only captured about a third of the associations of K10 with epigenetic markers and had virtually no influence on their interactive associations with mortality. While K10 is known to be positively associated with poorer health profiles, it is primarily related to mental health; our data would therefore suggest that the stronger interaction we observed for SRH was primarily driven by more physical than psychological aspects of health. Nevertheless, we highlighted through quantifying additive interactions that in terms of absolute risk, epigenetic age is a stronger marker of mortality risk for participants with higher levels of psychological distress. This indicates that psychological factors may play an important role in potentiating ageing-related declines in general health that are not captured by epigenetic markers of ageing. Taken together, these findings highlight that psychological indicators of health may have implications for the development of biological ageing markers that provide a more comprehensive picture of individualised ageing progress.

We used a relatively large sample of middle-aged and older adults to test the association of psychological distress with seven up-to-date epigenetic markers of ageing, depression, and inflammation. With the focus on psychological distress, our study generates insights into the link between global psychological symptoms in the general population and the ageing process. The K10 score we used is a reliable tool in assessing psychological distress and has been found to be predictive of the presence of a mental health disorder in older Australians (Anderson et al., 2013). Our study also provided an opportunity for external validation of epigenetic markers of depression, which were claimed to enhance depression prediction (Barbu et al., 2021).

The participants in our study were generally healthier than the general population and of white European origin (Giles and English, 2002), which could limit its generalisability. For example, individuals with very high levels of psychological distress were found to have lower screening participation rate (Anderson et al., 2023). Our study sample was somewhat older (mean age: 69 years) and included more males (69 %) than the studies that developed the epigenetic scores we considered, which may have some influence on their predictive value. The MCCS was initially carried out to study a wide range of research questions, primarily the link between lifestyle and the risk of cancer and other chronic diseases (Milne et al., 2017), and therefore lacked detailed self-reported data or clinical diagnoses on mental health disorders, which may mediate the association between psychological distress and epigenetic markers. Future studies may aim to disentangle the effects of global psychological symptoms and formal mental health disorders on epigenetic age, which would provide a more precise evaluation of the direct effect of psychological distress on ageing and health. Both psychological distress and methylation data were collected at only one time point, preventing conclusions on causality or temporality between psychological distress and molecular markers of health. Nevertheless, Welsh et al. examined K10 scores over up to eight years of follow-up in a large cohort of Australian adults, and concluded that despite some changes over time, psychological distress is relatively stable, therefore, a single estimate of the K10 score provides a reasonable proxy for chronic psychological distress (Welsh et al., 2020). While we adjusted for a range of confounding factors, except for BMI these were based on self-reported questionnaire administered during face-to-face visits, which may tend to overestimate the engagement in positive health behaviours and slightly influence the adjusted effect estimates. In addition, there may still be residual confounding due to genetic factors, early life experiences, medication use or medical conditions, for which the MCCS had limited available data, which may have contributed to the observed relationships between psychological distress, and the epigenetic markers.

The mechanisms underlying the association between psychological distress and epigenetic age are likely complex and not fully understood. Individuals with depression often exhibit chronic inflammation, which accelerates cellular ageing by inducing changes in DNAm patterns and histone modifications (Horsburgh et al., 2015). Oxidative stress, which occurs when there is an imbalance between the production of reactive oxygen species and the body's ability to neutralise them, is implicated in depression and may cause DNA damage and induce epigenetic changes (Pizzino et al., 2017). Wolkowitz et al. (2010) showed that alteration of stress-related pathways, such as the hypothalamic-pituitary-adrenal (HPA) axis, may cause epigenetic changes, including DNAm and histone modifications. An epigenome-wide association study by Wang et al. (2023a) identified 13 CpGs associated with optimism, which suggests DNAm as a possible marker of psychological health at the molecular level. To our knowledge, only few studies have investigated the biological mechanisms through which psychological distress affects DNA methylation patterns and ageing, which would shed light on lifestyle or other interventions that are likely to improve healthy ageing and well-being.

Our study has two main implications for psychological and ageing research. First, it emphasises the importance of addressing psychological distress to promote healthy ageing and interventions targeting mental well-being and coping strategies in the older population. Second, it highlights that the association of epigenetic ageing markers with health outcomes may vary by psychological factors, suggesting a complementary role for psychological/behavioural and precision medicine/molecular approaches for disease risk assessment.

5. Conclusion

In conclusion, higher levels of psychological distress were associated with older epigenetic age and higher *mCRP* levels. Participants with higher distress level and higher levels of epigenetic markers of ageing and *mCRP* had higher risk of mortality than others. These findings highlight the importance of early intervention on mental health issues in promoting healthy ageing and the potential synergistic effect of psychological and biological factors in prolonging lifespan.

CRediT authorship contribution statement

Danmeng Lily Li: Conceptualization, Formal analysis, Methodology, Writing – original draft. **Xiaojing Xu:** Conceptualization, Formal analysis, Writing – original draft. **Allison M. Hodge:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing. **Melissa C. Southey:** Data curation, Funding acquisition, Resources, Writing – review & editing. **Graham G. Giles:** Conceptualization, Funding acquisition, Resources, Writing – review & editing. **Roger L. Milne:**

Conceptualization, Funding acquisition, Methodology, Resources, Writing – review & editing. **Pierre-Antoine Dugué:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – original draft.

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Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2025.101090.

Data availability

Data may be made available on request.

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