Purpose in Life and Allostatic Load: A Systematic Literature Review

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Abstract

Introduction. Allostatic load (AL) serves as an objective measure for quantifying the adverse health consequences of chronic stress on the body. Purpose in life (PIL) is a malleable factor that potentially mitigates AL by facilitating bodily restoration after stress, and shows conceptual overlap with meaning in life (MIL) and sense of coherence (SOC). *Aims.* To guide future research on PIL's potential in mitigating AL, this review assessed the robustness and causality of the PIL-AL relationship, as well as mediating and moderating factors. *Methods.* This review received no funding and was preregistered in PROSPERO (ID: CRD42024512181). Cross-sectional and longitudinal studies examining the relationship between PIL, MIL, or SOC and at least one AL biomarker were obtained. The studies were sourced from PubMed, PsychINFO, Scopus, and Web of Science. Study quality was assessed with adapted versions of the Newcastle-Ottawa Scale (NOS) and the Jaccard Index was utilized to map the overlap of assessed AL biomarkers across studies. All data were narratively synthesized. *Results.* Among the 23 studies, most reported null findings regarding the PIL-AL relationship. PIL was differently related to individual AL biomarkers, which brings the use of AL as a unitary construct into question. The few studies that investigated moderators found inconsistent results, but health-promoting behaviors consistently mediated the PIL-AL relationship. However, comparing results was difficult due to heterogeneous measurement methods and assessed AL biomarkers and none of the studies were suitable for establishing causality, often lacked representative samples or did not assess PIL and AL at all study waves. *Conclusions.* Future studies with standardized procedures, experimental designs and improved methodological characteristics should assess PIL's relationship to individual AL biomarkers before definitive conclusions can be drawn through meta-analysis.

Keywords: Allostatic load; Physiological dysregulation; Chronic stress; Purpose in life; Meaning in life; Psychological well-being; Systematic literature review

List of Abbreviations

Abbreviation	Definition
AL	Allostatic Load
aSBP	Aortic Systolic Blood Pressure
BF	Body Fat
BMI	Body Mass Index
BP	Blood Pressure
Cat	Catecholamines
Chol	Cholesterol
Cort	Cortisol
CRP	C-Reactive Protein
Cys-C	Cystatin C
DHEA-S	Dehydroepiandrosterone-Sulfate
DBP	Diastolic Blood Pressure
E	Epinephrine
Fib	Fibrinogen
Gluc	Glucose
HbA1c	Glycosylated Hemoglobin
HDL	High Density Lipoprotein Cholesterol
HSP	High Frequency Spectral Power
HR	Heart Rate
ICAM-1	Intracellular Adhesion Molecule-1
IL-1β	Interleukin-1β
IL-1ra	Interleukin-1 Receptor Antagonist
IL-6	Interleukin-6
IL-10	Interleukin-10
LDL	Low Density Lipoprotein Cholesterol

MIL	Meaning In Life
MMP-9	Matrix Metalloproteinase-9
NE	Norepinephrine
NOS	Newcastle-Ottawa Scale
ELOC	External Locus Of Control
PIL	Purpose In Life
pSBP	Peripheral Systolic Blood Pressure
pDBP	Peripheral Diastolic Blood Pressure
RMSSD	Root Mean Square of Successive Differences
SBP	Systolic Blood Pressure
SDRR	Heart Rate Variability - Standard Deviation of R-R Intervals
sE-S	sE-Selectin
ILOC	Internal Locus Of Control
sICAM-1	Soluble Intercellular Adhesion Molecule-1
sIL-6R	Soluble Interleukin-6 Receptors
SOC	Sense Of Coherence
TGFβ-1	Transforming Growth Factor Beta 1
Tot/HDL	Total Cholesterol to High Density Lipoprotein Cholesterol Ratio
Trig	Triglycerides
We	Weight
Waist Circumference	WC
W/H	Waist-to-Hip Ratio

Purpose in Life and Allostatic Load: A Systematic Literature Review

AL, Allostasis and Homeostasis

McEwen (1998) defined allostatic load (AL) as the wear and tear on the body that results from chronic over- or inactivity of physiological systems in response to environmental challenges. Numerous studies have linked AL to adverse health outcomes, including cardiovascular diseases, diabetes, cancer and neurological and mental disorders (Guidi et al., 2020). Several biological systems, like the hypothalamic–pituitary–adrenal axis (HPA), the autonomic nervous system, the metabolic system and the immune system, are involved in responding to stressful stimuli (McEwen & Gianaros, 2010). This process, known as allostasis, is crucial for maintaining homeostasis - the body's ability to return to normal functioning after a threat. Efficient stress responses involve rapid mobilization and deactivation of these bodily systems when not needed. However, chronic stress disturbs this regulation, which leads to AL. In several phases, AL initiates biological changes that result in negative health outcomes (Carbone et al., 2022). First, chronic stress dysregulates stress hormones, termed primary outcomes (Rodriquez et al., 2019). These include (1) dehydroepiandrosterone sulfate (DHEA-S), (2) cortisol (COR), (3) epinephrine (E), and (4) norepinephrine (NE). Prolonged dysregulation of primary outcomes changes secondary outcomes, including (1) systolic blood pressure (SBP), (2) diastolic blood pressure (DBP), (3) waist–hip ratio (W/H), (4) high-density lipoprotein cholesterol (HDL), (5) total cholesterol, and (6) glycosylated hemoglobin (HbA1c). Aside from these "original" secondary outcomes, other researches also have included body mass index (BMI), c-reactive protein (CRP), and waist circumference (WC; Gustafsson et al., 2010; 2011). Eventually, these changes may result in physical diseases (e.g., cardiovascular and periodontal diseases, diabetes, cancer and musculoskeletal disorders) and mental disorders (e.g., mood, anxiety and trauma related disorders) - termed tertiary outcomes (Beckie, 2012; McEwen, 2002; McEwen, 2003).

Tertiary outcomes are considered distal, meaning they have a less immediate relationship with the core concept of AL, which is why they were not included in this study.

McEwen and Stellar (1993) suggested utilizing AL as a tool for predicting negative health outcomes by combining primary and secondary outcomes into one unitary construct. Recent work confirms that mental and physical systems are connected by proposing that some individuals possess a general susceptibility that makes them more likely to experience both mental and physical health issues (Brandt et al., 2023). However, the construct validity of AL is limited since studies show great variability in which biomarkers are employed and how AL is measured (McCrory et al., 2023; Carbone et al., 2022). For example, Juster et al. (2010) found that 51 different AL biomarkers were used to define AL across 58 studies in their review, indicating a lack of consensus, which complicates comparing findings across studies. To address this, McCrory et al. (2023) identified five AL biomarkers (CRP, HR, waist to height ratio, HDL, and HbA1c) that were most predictive of health outcomes such as grip strength, walking speed, and self-rated health. The authors propose that future research should focus on these biomarkers to enhance consistency. In sum, AL serves as an objective measure for quantifying the adverse health consequences of chronic stress, but its lack of construct validity usually hinders comparing results across studies.

PIL and its conceptual overlap with MIL and SOC

As individuals differ in their response to stressful situations (McEwen, 1998), attention is paid to malleable factors mitigating AL, with purpose in life (PIL) emerging as a promising target (Park et al., 2019; Zilioli et al., 2015). PIL reflects a perceived sense of life significance and direction (Burrow et al., 2024) and contributes to positive well-being (Yuen et al., 2015), cognitive functioning (Boyle et al., 2010), physical health (Kim et al., 2020) and greater longevity (Cohen et al., 2016). Moreover, Ryff (1989) emphasized that PIL is a

fundamental dimension of positive psychological well-being, alongside autonomy, environmental mastery, and personal growth. AshaRani and colleagues (2022) identified six ways to conceptualize PIL, including spirituality and religiousness, health and well-being, social relationships, meaningful aims and goals, mattering to others and inner strength. Among those, the majority of the literature used the concepts of health and well-being and meaningful aims and goals - definitions based on Viktor Frankl's work. Frankl (2006) defined PIL as the inner motivation and sense that life is worth living, even in extreme stress. This was based on his experiences in concentration camps, where he observed that survival depended on engagement in purposeful activities, rather than physical strength.

Having a PIL closely resembles having a sense of meaning in life (MIL) and sense of coherence (SOC). In terms of their connections, Martela & Steger (2016) stated that PIL and SOC are components of MIL, meaning that having a sense of PIL or SOC contributes to achieving MIL. The same authors state that MIL emerges from the connections, interpretations, aspirations, and evaluations that make our experiences comprehensible, as reflected by one's SOC, and direct our efforts toward desired futures, as reflected by one's PIL. On the one hand, PIL refers to being directed towards specific goals and represents the motivational aspect of MIL. Kashdan et al. (2023) clarified that PIL refers to having a far-reaching goal and a desire to achieve something beyond oneself, whereas MIL refers to the sense that life is meaningful, which can come from having goals. McKnight & Kashdan (2009) added that, while MIL occasionally drives PIL, PIL consistently contributes to MIL. On the other hand, SOC refers to being focused on understanding experiences, and represents the cognitive aspect of MIL (Martela & Steger, 2016). SOC allows purposeful individuals to understand, handle, and make sense of stressful situations, which enhances their coping abilities (Antonovsky, 1990).

Mechanisms explaining the PIL-AL relationship

In the literature, various explanations for a potential PIL-AL relationship are presented. First, PIL may affect how individuals perceive their environments, as those with a strong sense of PIL less likely perceive stimuli as stressful, possibly due to an enhanced SOC (Antonovsky, 1990). SOC helps individuals perceive events as less stressful by enhancing their understanding of them. Empirical studies among middle-aged women confirm that SOC significantly predicts AL, with meaningfulness playing a crucial role in linking SOC to AL (Lindfors et al., 2006). Moreover, purposeful individuals exhibit reduced reactivity to stressors, as they contextualize stressful stimuli within the broader and personally meaningful context of their life aims (Burrow et al., 2024). This ability to recenter focus from the present to overarching aims downregulates stress and facilitates return to homeostasis. An empirical study confirmed that participants with less PIL more likely overestimate the steepness of hills and the amount of effort necessary to climb them than participants with more PIL (Burrow et al., 2015). Furthermore, research by Hill and colleagues (2018) emphasized that having a PIL does not eliminate exposure to stressors, but mitigates their harmful consequences, as individuals with a strong PIL experience fewer increases in negative affect and physical symptoms on stressor days compared to stressor-free days. Thus, PIL likely facilitates understanding stressful situations and viewing challenges within the context of broader goals, thereby enhancing the ability to rebound from stressful experiences, which reduces AL.

Second, the extent of having a PIL influences an individual's internal locus of control (ILOC) and external locus of control (ELOC), which determines engagement in AL-reducing behaviors. A high ILOC reflects feelings of control over one's health and being the primary agent responsible for health outcomes, while a high ELOC refers to attributing health outcomes to external factors (Rotter, 1964). Shojaee & French (2014) showed that, among all researched mental health components, PIL had the highest positive correlation with ILOC.

Another study indicated that individuals with a high ILOC more likely adopt healthy lifestyle practices associated with lower AL rates (e.g., maintaining a balanced diet and exercising regularly; Suvarna et al., 2020). In sum, more PIL might be linked to lower AL via the adoption of health-promoting behaviors that protect against AL.

Moderators of the PIL-AL relationship

PIL and AL levels may vary depending on age. To illustrate, older adults seem to have less PIL because they face limited opportunities to pursue life goals (Mackenzie et al., 2018; Ryff, 1989; Springer et al., 2011) and have higher chronic inflammation levels compared to younger adults (Calder et al., 2017). Consequently, it could be more challenging for older adults to alleviate their high AL rates given their low PIL levels. Therefore, it is suggested that the PIL-AL relationship is weaker among older adults, compared to younger adults. Secondly, sex might moderate the PIL-AL relationship since sex moderated the relationship between positive affect, another psychological resource, and AL, in such a way that the relationship was stronger in women than in men (Schenk et al., 2018). Moreover, older women exhibit a stronger cortisol response to challenges than younger women, while this was not observed in men (Otte et al., 2005). Consequently, it is expected that the PIL-AL relationship is stronger among women, compared to men. Thirdly, the PIL-AL relationship may depend on clinical status, as depressive patients had significantly higher AL biomarker rates (Honkalampi et al., 2021), but lower PIL rates (Boreham & Schutte, 2023) compared to the general population. Possibly, patients' PIL rates are insufficient to protect against their heightened AL rates. Therefore, it is suggested that the PIL-AL relationship is weaker among clinical individuals compared to non-clinical individuals. In sum, age, gender and clinical status may moderate the PIL-AL relationship, with older adults, men and clinical samples exhibiting weaker relationships.

Current research

To foster further exploration of the potential benefits of PIL in mitigating negative health outcomes associated with stress, it is essential to pinpoint areas where additional research is needed and establish robust conclusions. Sutin and colleagues (2024) already expressed this interest by examining PIL's relationship with subjective stress, and showed that more PIL was related to less subjective stress. However, information from objective physiological measures like AL is also needed, as this contributes to a more comprehensive understanding, and objective measures do not suffer from the limitation of recall bias found in subjective instruments (Kokka et al., 2023). Although Guidi et al. (2020) explored the association between well-being and AL, they took a narrative approach and included only one study involving PIL. Therefore, this systematic literature review (SLR) consolidated and evaluated the reliability of existing knowledge regarding the PIL-AL relationship, guided by the research question: *"To which extent are PIL and AL related in adults in clinical and non-clinical samples, and which factors mediate and moderate this relationship?"* Specifically, the review delved into the significance, direction, and strength of the PIL-AL relationship and whether the current evidence supported causality. It was expected that higher PIL would be related to lower AL (Burrow et al., 2024; Lindfors et al., 2006; Shojaee & French, 2014; Suvarna et al., 2020). Age, sex and clinical status were investigated as potential moderators with the expectation that the PIL-AL relationship is weaker among older adults (Calder et al., 2017; Mackenzie et al., 2018; Ryff, 1989; Springer et al., 2011), men (Schenk et al., 2018; Otte et al., 2005) and clinical samples (Boreham & Schutte, 2023; Honkalampi et al., 2021). It was also expected that the ability to recenter focus from the present to overarching aims (Burrow et al., 2024) and adopting health-promoting behaviors mediated the PIL-AL relationship (Suvarna et al., 2020). Additionally, to guide interpretations of the results, the quality of the studies was evaluated, and, in anticipation of

the expected heterogeneity among studies (Carbone et al., 2022; Juster et al., 2010), it was exploratively investigated to what degree studies varied in their inclusion of AL biomarkers and methods of measurement of the five most studied AL biomarkers according to McCrory and colleagues (2023). Therefore, three additional secondary research questions were posed:

1. *"How should the quality of the studies investigating the PIL-AL relationship be evaluated?"*
2. *"To what degree did studies show overlap in which AL biomarkers were assessed?"*
3. *"To what degree did studies vary in how the five most studied AL biomarkers were measured?"*

Methods

Data collection

This systematic review was registered in the international prospective register of systematic reviews (PROSPERO) under ID #CRD42024512181 and conducted in accordance with the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) recommendations (Liberati et al., 2009). Ethical approval was not required, as this review synthesized data from previously published studies.

Search items were selected using the PICO (population, intervention, comparison, and outcome) approach (Aslam & Emmanuel, 2010). All searches were conducted in PubMed, PsychINFO, Scopus and Web of Science. Concerning the selected keywords, the aim was to include a multitude of synonyms for PIL and AL. This approach aligns with the recommendation to prioritize thoroughness over precision in the early stages of conducting a review, despite the potential of retrieving irrelevant articles (Wanden-Berghe & Sanz-Valero, 2012). The search terms were customized to each database, and, if possible, filters were used to exclude irrelevant articles. For example, the search results were limited to humans and

adults, and preprints, meta-analyses and reviews were excluded. Where possible, Boolean operators were used to construct search strings. Also, it was specified where the selected keywords had to appear in the articles. In the majority of databases, the requirement was restricted to the title, although, in situations where selecting the title option was not possible, keywords were permitted to appear in the abstract as well. No restrictions with respect to the year of publication were performed. Searches were conducted from January 20th to January 30th 2024. Backward searches (snowballing) of reference lists and forward searches (citation tracking) were performed to find additional records.

((“allostatic load” OR allosta* OR “chronic stress” OR “stress biomarkers” OR “physiological dysregulation” OR “physical imbalance” OR “physiological adaptation” OR “physiological response” OR “physiological stress” OR autonomo* OR metaboli* OR immun* OR cardio* OR “oxidative” OR “adrenal” OR “HPA axis” OR “heart rate variability” OR “inflammation” OR “sympathetic nervous system” OR “dehydroepiandrosterone sulfate” OR “cortisol” OR “epinephrine” OR “norepinephrine” OR “systolic blood pressure” OR “diastolic blood pressure” OR “waist–hip ratio” OR “high-density lipoprotein cholesterol” OR “total cholesterol” OR “apolipoprotein A1” OR “apolipoprotein B” OR “body mass index” OR “C reactive protein” OR “waist circumference”) AND (“purpose in life” OR “ikigai” OR eudaimon* OR “purposeful engagement” OR “psychological resources” OR “meaning in life” OR “sense of purpose” OR “life purpose” OR “sense of meaning” OR “psychological well-being” OR “happiness” OR “resilience” OR “flourishing” OR “fulfillment” OR “self-realization” OR “ambition” OR “calling” OR “life meaning” OR life aim* OR “life goals” OR “positive health” OR “life quality” OR “spirituality” OR “vocation” OR “goal engagement” OR “goal-setting”))

Study selection was performed by one reviewer (DSR) using Covidence software (Veritas Health Innovation, n.d.). Collected studies were in- or excluded based on the criteria summarized in Table 1. Following the elimination of duplicates, the articles underwent screening based on their title and abstract, and an examination of the full text. If a full text was unavailable, this was requested from the corresponding author. Exclusion reasons were documented throughout this process and described in Figure 1. When in doubt whether a study met the inclusion criteria, the second collaborator (JPS) reviewed the study.

Table 1

Inclusion and exclusion criteria following the PICO process

PICO elements	Inclusion	Exclusion
Population	● Studies based on healthy populations as well as clinical/patient populations	● Studies on animals ● Studies on individuals below 18 y/o
Intervention	Not applicable	
Comparison	Not applicable	
Outcome	● Studies that assessed AL through the physiological measurement of at least one primary or secondary AL mediator. ● The study assessed both AL (*preferably operationalised as allostatic load. In case of absence, measures of independent AL biomarkers were used*) and PIL (*preferably operationalised as purpose in life. In case of absence, measures of meaning in life or sense of coherence were used due to their conceptual overlap with PIL).*	● Studies using subjective AL measurements (e.g., self-reported questionnaires) ● Studies addressing AL without specifically measuring chronic stress, such as those inducing participants to stressful situations (e.g., Trier Social Stress Test) ● Studies that exclusively measured AL as a disease status such as diabetes or cancer
Study design	● Studies that used a cross-sectional design or an observational longitudinal design.	● Studies with only qualitative data ● Publications which did not constitute primary original empirical research (e.g. reviews,

	meta-analyses and books)
Other	• No full text available upon request • Studies that received private funding • No English/Dutch translation available upon request • Necessary data was not reported/retrievable upon request • Studies that were not published in peer-reviewed journals

Data extraction

Data extraction was performed by one reviewer (DSR) using Microsoft Excel. First, relevant data was manually extracted from each study and categorized in a table with nine columns: title and author details; study design; participant characteristics, including sample-size, mean age, sex ratio, race and whether it was a clinical or non-clinical sample; measure of PIL; measured AL biomarkers, including total number and the level of identified biomarkers (primary or secondary mediators); methods of AL biomarker assessment; moderators/mediators; covariates. In case of missing data, the authors were emailed. In case of a non-response, the study was excluded. In the Supplementary Materials (S3 Table and S4 Table), two additional tables are dedicated to cross-sectional and longitudinal studies, where the coefficients are organized according to their characteristics. This involved specifying whether the coefficients related to primary or secondary AL biomarkers and identifying the systems to which these biomarkers belonged (e.g., cardiovascular, metabolic, inflammatory, neuro-endocrine, or other systems).

Estimation of Bias in the Collected Data

To assess study quality, two versions (for both longitudinal and cross-sectional studies) of the Newcastle-Ottawa Scale (NOS) were employed, a widely recognized tool for evaluating non-randomized studies in meta-analyses and systematic reviews (Wells et al., 2011). The NOS for longitudinal studies was adapted by removing one item concerning the selection of non-exposed cohorts, as none of the studies included non-exposed cohorts. Afterwards, the scale consisted of seven items across three domains: study group selection, group comparability, and outcome assessment. For cross-sectional studies, an adapted version with six items across the same domains was employed, as utilized by Patra et al. (2015). Adaptations involved substituting items specific to longitudinal studies, such as inquiries about follow-up duration, with questions pertaining to the employed statistical tests. Eventually, study quality was assessed through a star system. Longitudinal studies were scored between zero and eight stars, while cross-sectional studies were scored between zero and seven stars. Longitudinal studies with three stars or less were deemed low quality, four to six stars as moderate quality, and seven or more as high quality. For cross-sectional studies, two stars or less indicated low quality, three to five denoted medium quality, and six or more stars indicated high quality. One reviewer (DSR) independently conducted the assessment, detailed in Tables S1 and S2, with any uncertainties resolved through discussion with the second collaborator (JPS).

Data analysis

First, the overlap among the assessed AL biomarkers across the included studies was calculated by using the Jaccard Index, a similarity coefficient for binary data ranging from zero (indicating no overlap among scales) to one (signifying complete overlap). The Jaccard similarity coefficients were computed by modifying the code originally developed by Fried

(2017). While Fried's work centered on patient-reported outcome measures, the formula was adjusted to suit studies and their AL measurement. The utilized formula was (s/(u1+u2+2)), where 's' indicates the shared number of AL biomarkers between two studies, and 'u1' and 'u2' represents the number of unique AL biomarkers in those studies. Due to the absence of a widely accepted guideline for interpreting the Jaccard similarity coefficient, the classification from Evans (1996) was adopted: very weak (0.00-0.19), weak (0.20-0.39), moderate (0.40-0.59), strong (0.60-0.79), and very strong (0.80-1.0). Analyses were conducted using R. The data and the code are accessible in the Supplementary Materials.

To guide the interpretation of the results, the studies' characteristics were narratively synthesized, including the number of included cross-sectional and longitudinal studies, the number of studies involving clinical populations and their conditions, the predominant sex and age group, the country of origin prevalent in the studies, and the utilized instruments to measure PIL, MIL or SOC. Based on the data extraction forms, the possibility of conducting a quantitative synthesis was ruled out because the studied populations and methods of measurement did not share sufficient similarity across studies. Therefore, all data were narratively synthesized by one reviewer (DSR). To increase transparency and reproducibility, the synthesis process was based on the framework of Rodgers and colleagues (2009), which includes elements of a narrative synthesis when a statistical synthesis is not possible. The first stage was omitted as decisions about the scope and eligibility of studies had already been established. In the second stage, a preliminary synthesis was developed by producing textual descriptions on each included study. Then, groupings and clusters were made, meaning that the included studies were organized into smaller groups based on the research questions to make the process manageable and identify potential moderating effects. The studies were grouped based on: whether they primarily examined clinical or non-clinical individuals, the predominant gender and age-group (<65 years and >65 years) of the examined population,

whether it was a cross-sectional or longitudinal study and identified moderators/mediators. Vote counting was applied as a descriptive tool by using ticks where the PIL-AL relationship appeared significant, how the strength of the found relationship could be categorized (as either weak, moderate or strong) and which direction the relationship points to. In the third stage, the reviewer integrated findings by composing textual summaries, organized based on the opposed research questions.

Results

Study characteristics

A total of 23 studies met the inclusion criteria. The screening process has been summarized in Figure 1 and the characteristics of included studies have been described in Table 2.

Figure 1

PRISMA Flow Diagram

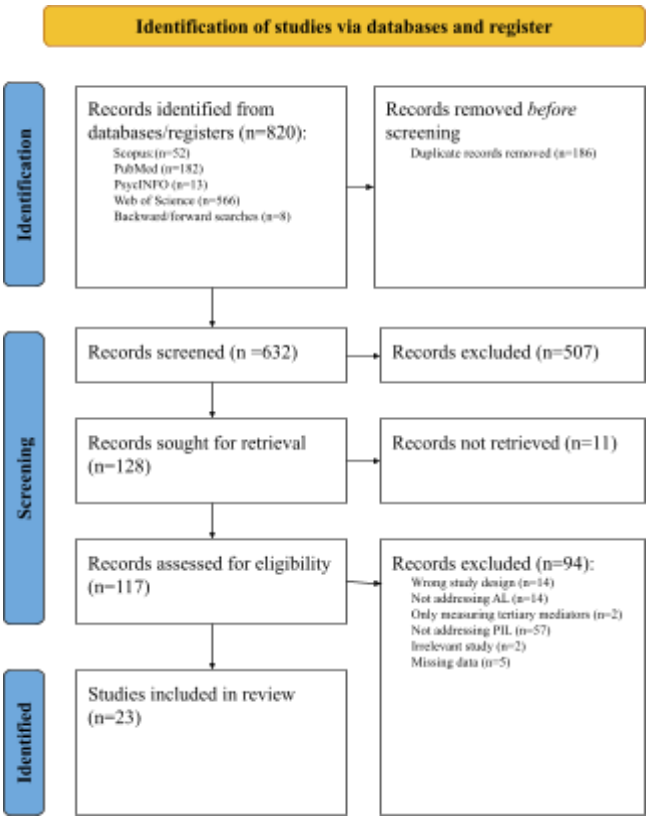


Table 2

Characteristics of Included Studies

Study	Country	Study design	Participant characteristics	PIL measure	AL biomarkers	Methods of biomarker assessment	Mediators (med)/ moderators (mod)	Covariates
1. Berkowitz et al. (2023)	U.S., Chile	Cross-sectional	Non-clinical: Female (N=1126) Male (N=934) <50 years (N=692) 50-65 years (N=891) >65 years (477) Mage=55.6 Clinical: Female (N=130) Male (N=93) <50 years (N=144) 50-65 years (N=71) >65 years (8) Mage=46.6	PIL	N=1 WC (2)	• WC was measured in cm by the staff of clinical research centers.	Healthy eating (med)	Sex Age Race Education Physical activity
2. Boylan & Ryff (2015)	U.S.	Longitudinal	Non-clinical: Female (N=469) Male (N=295) Age range=35-86 Mage=57.2 Clinical: Female (N=217) Male (N=224) Age range=37-85 Mage=58.0	PIL	N=6 DBP (2) Gluc (2) HDL (2) SBP (2) Trig (2) WC (2)	• Waist was measured at the narrowest point between ribs and iliac crest. • BP was assessed in a seated position 3 times with a 30 sec interval. The two most similar readings were averaged. Beforehand, participants rested for 5 min. • The lipid panel and glucose were assessed from a fasting blood sample.	-	Age Sex Educational attainment Race Marital status Current smoking status Alcohol consumption Physical activity Medication usage
3. Campos-Uscanga	Mexico	Cross-	Non-clinical	PIL	N=1	• Weight was measured with a Taylor precision scale after bladder	-	-

et al. (2022)		sectional	Female (N=111) Mage=20.40		BMI (2)	evacuation, barefoot and wearing very little clothing. Height was measured with nothing on their heads and with a Seca ™ precision stadiometer. Measurements were taken by 5 trained nutritionists and data were collected using standardized examination procedures.		
4. Davis et al. (2015)	U.S.	Cross-sectional	Clinical Female (N=365) Mage=59.76	PIL	N=1 NE (1)	• Frozen tumor samples were pulverized, homogenized, and extracted before immediate measurement of catecholamine levels using high-performance liquid chromatography with electrochemical detection.	-	Physical well-being Stage of disease Histology Psychological treatment history Beta-blocker use Cafeïne use
5. Friedman et al. (2007)	U.S.	Cross-sectional	Non-clinical Female (N=135) Age=61-91 Mage=74.02	PIL	N=11 Cor (1) DBP (2) E (1) HDL (2) HbA1c (2) IL-6 (2) NE (1) SBP (2) sIL-6R (2) Tot/HDL (2) W/H (2)	• Blood samples were obtained by standard phlebotomy techniques in participants' homes and were stored at -80°C. • IL-6 and sIL-6R concentrations were measured in duplicate with enzyme-linked immunosorbent assay. • SBP and DBP were measured three times after 5 min of quiet sitting, and the average of the two most similar was calculated. • Fasting blood samples for assays of HDL cholesterol, total cholesterol, and glycosylated hemoglobin were obtained during the participants' overnight stay at the GCRC.	-	Age Years of education, Average pretax household income Marital status Health status Health behavior, Neuroendocrine measures Anti-inflammatory medication use
6. Friedman & Ryff (2012)	U.S.	Longitudinal	Clinical Female (N=565) Male (N=463) Mage=58	PIL	N=4 BMI (2) CRP (2) IL-6 (2) W/H (2)	• Serum IL-6 from fasting blood samples was measured using a high-sensitivity enzyme-linked immunosorbent assay according to the manufacturer's guidelines. • CRP was measured using a particle-enhanced immunonephelometric assay.	Number of chronic conditions (mod)	Age Sex Marital status Educational attainment Race Obesity Use of medication Negative affect
7. Giannis et al. (2023)	Canada	Longitudinal	Non-clinical Female (N=69) Male (N=60) Age range=60-83	PIL	N=2 CRP (2) BMI (2)	• A single use lancet was used to obtain up to 3 drops of blood, which were collected on filter paper. The samples were allowed to dry and were then stored in a freezer. They were sent to Northwestern University, where a high sensitivity enzyme immunoassay was utilized.	Age (mod)	Sex BMI Chronic illness SES

			Mage=77.51					Medication use
8. Gouin et al. (2017)	Canada	Cross-sectional	Non-clinical Female (N=152) Male (N=22) Age range=50-57 Mage=50.29	MIL	N=2 CRP (2) IL-6 (2)	• IL was measured using an electrochem magiluminescence method with ultra-sensitive kits purchased from Meso Scale Discovery. Plates were read using the Meso Scale Discovery Sector Imager 2400. • CRP was analyzed using chemiluminescence methodology with the Immulite 1000.	Adverse childhood experiences (med)	Age Sex Race BMI Depressive symptoms Perceived stress Antidepressant medication Self-reported medical conditions
9. Guimond et al. (2022)	U.S.	Longitudinal	Non-clinical Female (N=56) Male (N=44) Age range=60-78 Mage=69	PIL	N=1 CRP (2)	• Blood spot samples were obtained after cleaning the fingers with an alcohol prep pad, pricking a finger with a sterile lancet, and collecting blood droplets on a blood spot card. The card was air-dried, placed in a foil pouch, and mailed to the University of Vermont where assays for high-sensitivity CRP were conducted. An enzyme-linked immunosorbent assay was used.	Sex (mod) Age (mod)	Race Marital status Educational attainment Total wealth Labor force participation Health insurance coverage Smoking status Physical activity Alcohol consumption Sleep problems BMI
10. Hsiao et al. (2014)	China	Longitudinal	Clinical Female (N=34) Age range=21-63 Mage=49.6 Non-clinical Male (N=34) Age range=35-70 Mage=53.7	MIL	N=1 Cor (1)	• Participants collected salivary cortisol responses using neutral cotton Salivette tubes in their homes at 6 time points after being instructed about collection and storage procedures. Samples were collected only once on a weekday at each measurement point. Participants could not brush their teeth before completing the first saliva sampling of the day and not eat before the first 3 collections. For the remaining 3 samples, participants were asked not to eat during 30 min before samples were collected.	-	-
11. Ironson et al. (2018)	U.S.	Cross-sectional	Non-clinical Female (N=379) Male (N=264) Mage=66.10	MIL	N=1 CRP (1)	• A blood sample was collected via a capillary finger stick with a disposable lancet. Between three and five blood spots were applied to filter paper and shipped to the University of Washington where a high-sensitivity assay was used.	-	Age Sex Education BMI

								Smoking Alcohol use Social support
12. Lee et al. (2022)	South-Korea	Cross-sectional	Older adults: Non-clinical Female (N=41) Male (N=34) Mage=75.60 Younger adults: Non-clinical Female (N=54) Male (N=73) Mage=22.98	PIL	N=3 CRP (2) IL-1B (2) IL-6 (2)	• Saliva samples were collected using passive drool. Participants could not eat food for 60 min and rinsed their mouths for 10+ min before collection. Using a Saliva Collection Aid connected to a collection vial, participants were asked to pull saliva into the mouth and then fill the saliva into the collection vial to 1 ml. Samples were stored at 20°C. Levels of IL-1ß, IL-6, and CRP were quantified using immunosorbent assay kits.	Age (mod)	Sex Education BMI Health-related behavior Illness symptoms Anti-inflammatory medicine treatment Biological plausibility
13. Lewis & Hill (2023)	U.S., England	Longitudinal	HRS: Non-clinical Female (N=3979) Male (N=2074) Mage=66.69 ELSA: Non-clinical Female (N=182) Male (N=156) Mage=65.72	PIL	N=11 BMI (2) Chol (2) CRP (2) Cys-C (2) DBP (2) Fib (2) Gluc (2) HbA1c (2) HDL (2) SBP (2) Trig (2)	• SBP and DBP were measured using Omron brand HEM-780 and HEM 907 automated blood pressure monitors. Participants sat quietly for 5 min prior to measurement. 4 measurements were taken in a seated position. • BMI in HRS was computed as weight in kg divided by squared height in m from self-reported height and weight at each wave, and from height and weight measured by a certified nurse in ELSA. • In HRS, dried blood spots were collected using a BDlancet and two filter paper collection cards, whereas in ELSA 24 ml fasting blood draws were collected for respondents under 80 years of age by nurses.	-	Age Sex Education in years Race Number of depressive symptoms
14. Lindfors & Lundberg (2002)	Sweden	Cross-sectional	Non-clinical Female (N=12) Male (N=14) Age range=24-62 Mage=N.D	PIL	N=6 Cat (2) Cor (1) DBP (2) E (1) NE (1) SBP (2)	• Daytime levels of SBP and DBP were measured with an automatic digital blood-pressure device (Blood Pressure Monitor, DS-140). . • Beginning immediately after awakening, urinary catecholamines were collected. • Cor was measured by collecting saliva samples in a standard centrifugation tube containing a small cotton roll that is chewed for a few min to obtain a sufficient amount of saliva. Participants could not brush their teeth, drink, smoke or eat 15 min before sampling. Samples were collected at the end of each day and frozen until centrifuged and analyzed for cortisol by radioimmunoassay.	-	-
15. Marteinsdottir et al. (2016)	Sweden	Cross-sectional	Non-clinical Female (N=473)	SOC	N=9 BMI (2)	• Participants' weight and height were obtained during visits and used for calculating BMI.	-	Age Sex

			Male (N=471) Age range=45-69 Mage=57		CRP (2) DBP (2) Gluc (2) HDL (2) IL-6 (2) LDL (2) MMP-9 (2) SBP (2)	• SBP and DBP were measured 3 times in a sitting position after 5 min of rest by using the Omron M5-1 digital. The mean of the 2nd and 3rd measurements was used. • Blood lipids and glucose were analyzed directly after sample collection using the ADVIA 1650 and Hemocue glucose system. • IL-6 was measured in EDTA plasma using Ultrasensitive Bead Kit Technology on a Luminex 100 System. • CRP was measured in plasma by a highly sensitive latex-enhanced turbidimetric immunoassay. • MMP-9 was measured in EDTA plasma using human Biotak ELISA systems.		Medical conditions Cardiovascular risk factors
16. Pulopulos et al. (2018)	U.S.	Cross-sectional	Study 1: Non-clinical Female (N=90) Male (N=82) Mage=37.7 Age range=21-55 Study 2: Non-clinical Female (N=134) Male (N=125) Mage=28.9 Age range=18-54	PIL	N=1 Cor (1)	• Salivary samples were collected using Salivettes. Beforehand, participants could not eat or brush their teeth for one hour, and they abstained from smoking for 30 min before collection time. Participants received the salivettes and detailed instructions and either a handheld computer (study 1) or a preprogrammed wristwatch (study 2) to alert them at each collected time.	Perceived stress (med)	Age Sex BMI Education Race
17. Ryff et al. (2006)	U.S.	Cross-sectional	Non-clinical Female (N=135) Age range=61-91 Mage=74	PIL	N=9 Cor (1) DBP (2) DHEA-S (1) E (1) HDL (2) HbA1c (2) NE (1) SBP (2) W/H (2)	• Blood samples and 12-hour urine samples were obtained. • Urinary free cortisol levels were measured by radioimmunoassay. • Urinary E and NE were measured via liquid chromatography. • Subjects provided saliva samples 3 times a day for 4 days at home. The first sample was collected in the morning 30 min after awakening, but before brushing teeth, drinking coffee or eating. The second sample was collected at midday before eating, and the third sample in the evening before brushing teeth. Cor levels were measured with the Salimetrics cortisol enzyme immunoassay kit. Prior to the assay, samples are centrifuged for 10 min at 5,000 rpm. • W/H was calculated on the basis of WC and hip circumference. • SBP and DBP were calculated as the average of 3 BP readings after 5 min of quiet sitting. • Fasting blood samples for assays of HDL, chol and HbA1c were obtained before 7: 00 AM during the overnight stay.	-	Medication use
18. Sutin et al. (2023)	U.S.	Prospective cohort study	Non-clinical Female (N=5362) Male (N=3637)	PIL	N=6 CRP (2) IL-1ra (2)	• Venous blood samples were collected, centrifuged in the field, and shipped overnight to the University of Minnesota. • CRP was measured using a latex-particle enhanced immunoturbidimetric	Episodic memory (med)	Age Sex Race

			Mage=67.48		IL-6 (2) IL-10 (2) sTNFR1 (2) TGFβ-1 (2)	assay kit. • A cytokine panel was used to measure IL-6, IL-10, IL-1ra, sTNFR1, and TGFβ-1. These measures were derived from ELISA Simple Plex Assay on the ELLA System from Protein Simple.		Ethnicity Education
19. Svartvik et al. (2000)	Sweden	Observational study	Non-clinical Female (N=450) Mage=55.17	SOC	N=9 BMI (2) DBP (2) Chol (2) Gluc (2) HDL (2) LDL (2) SBP (2) Trig (2) We (2)	• Weight and height were measured without shoes. • WC was measured at the umbilical level and hip circumference at the widest part. • BP was measured twice in the supine position after 10 min of rest and a mean figure was registered. • Non-fasting blood samples were drawn for serum lipoproteins (chol, HDL, LDL, trig) and glucose. The LDL/HDL ratio was calculated. Lipids were determined with a Cholestech LDX® instrument, and glucose using a HemoCue® device.		Age BMI Smoking Educational level Quality of life score Number of medical symptoms
20. Tanaka et al. (2011)	Spain	Cross-sectional	Non-clinical Male (N=37) Mage=24.8	SOC	N=12 BF (2) BMI (2) BP (2) CRP (2) DBP (2) HbA1c (2) HDL (2) IR (2) SBP (2) Tot/HDL (2) Trig (2) W/H (2)	• The measurement took place in a tranquil laboratory environment maintained at a temperature range of 24–26°C. Initially, the FPG device was affixed, followed by a minimum resting period of 3 min before commencing FEI measurement trials lasting 4 min. These measurements were conducted with the participant seated, their left hand positioned approximately at heart level. The CAVI assessment occurred with the participant lying down after a 3-minute resting period, aligning with their resting BP just before or after the FPG measurement on the same day. • A blood sample was drawn from the antecubital vein in the morning after a 10-hour overnight fast, excluding medications, within a week of the FPG and CAVI measurements. • Standard methods were employed to measure BMI and W/H, while BF was determined through bioelectrical impedance analysis using InnerScan. • Serum TC (mg/dL) was measured using the UV-end method with cholesterol dehydrogenase, HDL (mg/dL), and LDL (mg/dL) were determined using homogeneous methods, while TG (mg/dL) levels were assessed using an enzymatic assay on an autonomic chemistry analyzer (AU5400, Beckman Coulter Inc.). • HbA1c was quantified via high-performance liquid chromatography (HPLC), plasma glucose using GOD-amperometry, and IR was measured employing a chemiluminescent enzyme immunoassay on the Lumipulse Presto System. IR was calculated using the formula: (fasting plasma insulin concentration - fasting glucose concentration)/405. • CRP levels were determined using ultrasensitive latex nephelometry with	-	Age

						an autonomic analyzer, featuring a lower detection limit of 0.05 mg/L. • SBP and DBP were measured from the middle portion of the left third finger using a Finapres system (Ohmeda 2300, Ohmeda Monitoring Systems.		
21. Thege et al. (2015)	Spain	Cross-sectional	Clinical: Female (N=67) Male (N=71) Mage=65.3 Non-clinical: Female (N=228) Male (N=93) Mage=42.6	MIL, SOC	N=3 aSBP (2) pDBP (2) pSBP (2)	• aSBP was assessed at the aortic trunk.	-	Sex Age Educational level
22. Woo et al. (2020)	U.S.	Longitudinal	Non-clinical Female (N=474) Male (N=376) Age range=34-83 Mage=54.73	PIL	N=23 Cor (1) CRP (2) DBP (2) DHEA-S (1) E (1) Fib (2) Gluc (2) HbA1c (2) HDL (2) HR (2) HSP (2) IL-6 (2) IR (2) LDL (2) LSP (2) NE (1) RMSSD (2) SBP (2) SDRR (2) sE-S (2) sICAM-1 (2) Trig (2) W/H (2)	• Clinical nursing staff collected a 12-hr urine specimen and fasting blood specimen. All biomarker levels were quantified in duplicate, and values were determined by standard procedures. • CRP, fib and IL-6 were assessed by blood specimens. CRP was assessed by a particle enhanced immunonephelimetric assay using the BNII nephelometer. Fib was also measured by the BNII nephelometer. IL-6 was assessed by a high-sensitivity enzyme-linked immunosorbent assay (ELISA). • Cor, E and NE were assessed by urine specimens. Cor was assessed by Enzymatic Colorimetric Assay and Liquid Chromatography-Tandem Mass Spectrometry. E and NE were assessed by a High-Pressure Liquid Chromatography (HPLC).	-	Age Race Marital status Sex Education Number of chronic conditions
23. Zilioli et al. (2015)	U.S.	Longitudinal	Non-clinical Female (N=549)	PIL	N=20 BMI (2)	• Clinical nursing staff collected a 12-hr urine specimen and fasting blood specimen. All biomarker levels were quantified in duplicate, and values	Internal locus of control	Age Gender

	Male (N=436) Mage=46.14	Cor (1) CRP (2) DBP (2) DHEA-S (1) EP (1) Fib (2) Gluc (2) HbA1c (2) HDL (2) HR (2) ICAM-1 (2) IL-6 (2) IR (2) LDL (2) NE (1) RMSSD (2) SBP (2) SDRR (2) W/H (2)	were determined by standard procedures. • CRP, fib and IL-6 were assessed by blood specimens. CRP was assessed by a particle enhanced immunonephelimetric assay using the BNII nephelometer. Fib was also measured by the BNII nephelometer. IL-6 was assessed by a high-sensitivity enzyme-linked immunosorbent assay (ELISA). • Cor, E and NE were assessed by urine specimens. Cor was assessed by Enzymatic Colorimetric Assay and Liquid Chromatography-Tandem Mass Spectrometry. E and NE were assessed by a High-Pressure Liquid Chromatography (HPLC). • Both SBP and DBP were recorded using a Finometer monitor (Finapres Medical Systems). • Total cholesterol, HDL cholesterol, and triglyceride levels were determined using enzymatic colorimetric assays.	(med) External locus of control (med)	Education Ethnicity Current PIL Positive affect Negative affect Positive relations with others

Note. Biomarker abbreviations: aSBP: aortic systolic blood pressure, BF: body fat, BMI: body mass index, BP: blood pressure, Cat: catecholamines, Chol: cholesterol, Cort: cortisol, CRP: c-reactive protein, Cys-C: cystatin c, DHEA-S: dehydroepiandrosterone-sulfate, DBP: diastolic blood pressure, E: epinephrine, Fib: fibrinogen, Gluc: glucose, HbA1c: glycosylated hemoglobin, HDL: high density lipoprotein cholesterol, HSP: high frequency spectral power, IR: insulin resistance, HR: heart rate, ICAM-1: intracellular adhesion molecule-1, IL-1β: interleukin 1β, IL-1ra: interleukin-1 receptor antagonist, IL-6: interleukin-6, IL-10: interleukin-10, LDL: low density lipoprotein cholesterol, LSP: low-frequency spectral power, MMP-9: matrix metalloproteinase-9, NE: norepinephrine, pSBP: peripheral systolic blood pressure, pDBP: peripheral diastolic blood pressure, RMSSD: root mean square of successive differences, SBP: systolic blood pressure, SDRR: heart rate variability - standard deviation of R-R intervals, sE-S: sE-Selectin, sICAM-1: soluble intercellular adhesion molecule-1, sIL-6R: soluble IL-6 receptors, sTNFR1: soluble tumor necrosis factor receptor 1, TGFβ-1: transforming growth factor beta 1, Tot/HDL: total cholesterol to high density lipoprotein cholesterol ratio, Trig: triglycerides, We: weight, WC: waist circumference, W/H: waist-to-hip ratio. Following each biomarker, its level is indicated within brackets: (1) as a primary mediator, (2) as a secondary mediator.

Among the 23 studies, nine conducted longitudinal research, while 14 utilized cross-sectional designs. Clinical participants were included in nine studies, encompassing 2.229 patients with metabolic syndrome, cancer, obesity, or cardiovascular disease, whereas 22 studies included a total of 23.921 non-clinical participants. Females predominated in 86.96% of the studies. Five studies exclusively focused on females and one on males. Geographically, 15 studies originated from the U.S., three from Spain, two from Sweden and Canada, and one each from Chile, Mexico, China, South Korea, England, and Germany. PIL was measured in 17 studies, with sixteen using the PIL subscale of the Ryff's Psychological Well-Being Scale (Ryff, 1989) and two using the Life Engagement Test (Scheier et al., 2006). MIL was assessed in four studies with the Meaning in Life Questionnaire (MLQ; Steger et al., 2006), the life meaning subscale from the Brief Stress and Coping Inventory (Thege et al., 2008), the meaningfulness subscale of the Essen Resource Inventory (Tagay et al., 2014), and the meaningful engagement subscale of the REMAP scale (including relational engagement, emotional sensibility, meaningful action, awareness of self and others, and physical health behaviors; Malarkey et al., 2016). Gouin and colleagues (2017) assessed meaningful engagement without a validated questionnaire. SOC was measured in four studies by using the Orientation to Life Questionnaire by Antonovsky (1993).

Study quality

Two versions of the NOS were used to appraise the quality of the 23 included studies with a star system, detailed in the Supplementary Materials (S2 Table). For the 14 cross-sectional studies, star ratings ranged from three to six. None were low quality; 57.10% were average, and 42.90% were high quality. In total, 71.40% of the studies did not meet the criteria for a representative sample. Typically, the sample was a select group, or there was no information provided on sample recruitment. Additionally, 71.40% of the studies did not

provide information on non-respondents, preventing a comparison between respondents and non-respondents. All studies received a star for the remaining criteria.

For the nine longitudinal studies, the number of assigned stars ranged from two to eight. One study was deemed low quality, while 66.66% were classified as average, and 22.22% as high. Overall, 66.66% of the longitudinal studies did not measure PIL or AL at all study waves, making it impossible to confirm that the outcome of interest was not present at baseline. Additionally, 77.70% of the studies lacked representative samples or had small sample sizes. However, most studies had adequate follow-up periods.

Biomarker assessment

Overlap of assessed AL biomarkers. Results from the Jaccard Index analysis, as shown in Table 3, demonstrated that 38 different biomarkers were assessed. The five most studied biomarkers were CRP, IL-6, DBP, SBP and HDL. The overall similarity correlation was 0.12, which was categorized as very weak. Figure 2 shows the overlap of the AL biomarkers across the 23 included studies, categorized as primary and secondary outcomes.

Table 3

Correlation table according to the Jaccard Index

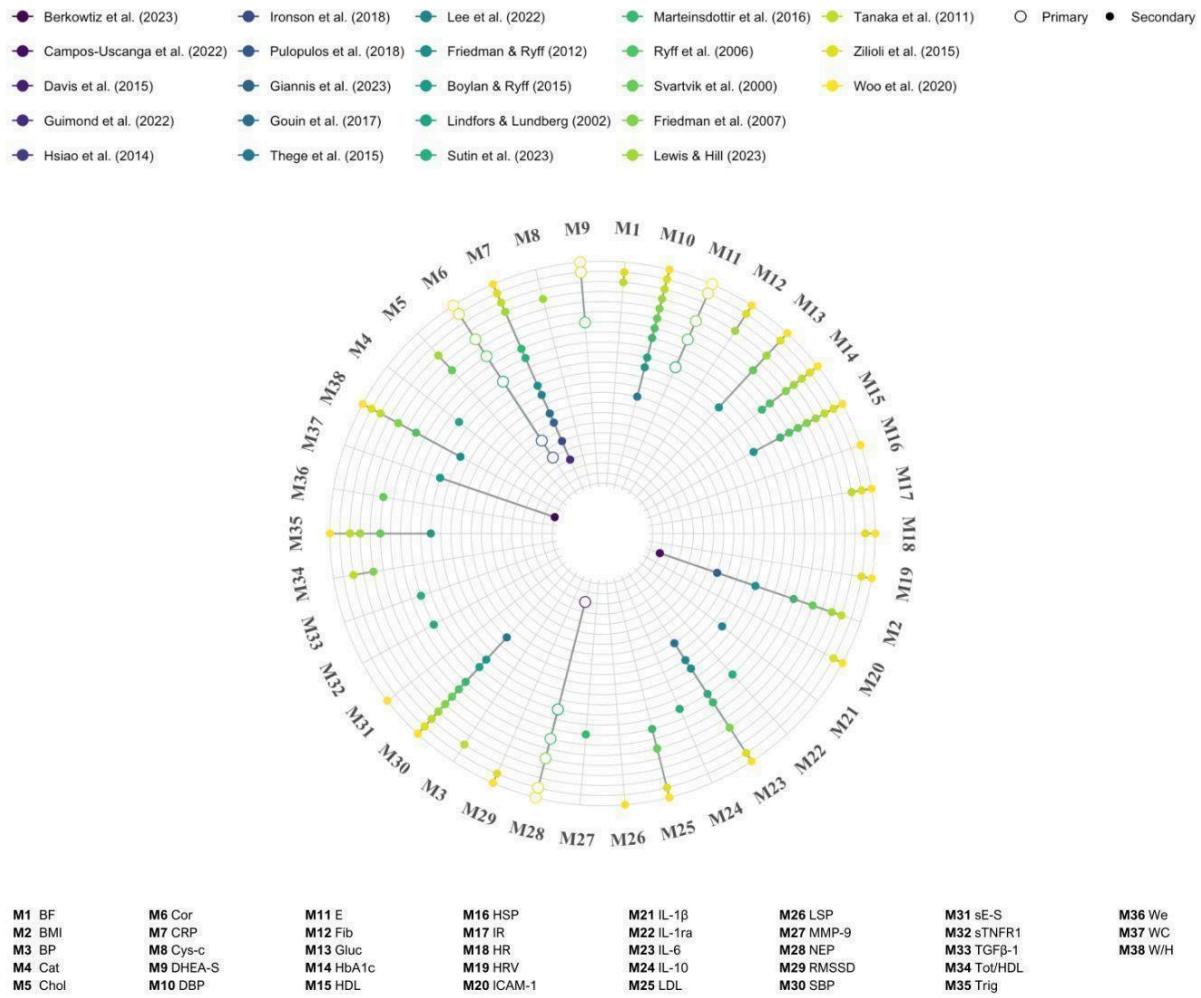
	Ber. 2023	Boy.2015	Cam. 2022	Dav. 2015	Frie. 2007	Frie. 2012	Gia. 2023	Gou. 2017	Gul. 2022	Hsi. 2014	Iro. 2018	Lee. 2022	Lew. 2023	Lin. 2002	Mar. 2016	Pul. 2018	Ryf. 2006	Sut. 2023	Sva. 2000	Tan. 2011	The. 2015	Woo. 2020	Zil. 2015
Ber. 2023	1																						
Boy. 2015	0.17	1																					
Cam. 2022	0	0	1																				
Dav. 2015	0	0	0	1																			
Frie. 2007	0	0.23	0	0.1	1																		
Frie. 2012	0	0	0.25	0	0.17	1																	
Gia. 2023	0	0	0.5	0	0	0.5	1																
Gou. 2017	0	0	0	0	0.09	0.5	0.33	1															
Gui. 2022	0	0	0	0	0	0.25	0.5	0.5	1														
Hsi. 2014	0	0	0	0	0.1	0	0	0	0.5	1													
Iro. 2018	0	0	0	0	0	0.25	0.5	0.5	0	0	1												

Lee. 2022	0	0	0	0	0.08	0.4	0.25	0.67	0.33	0	0.33	1											
Lew. 2023	0	0.42	0.09	0	0.24	0.15	0.18	0.08	0.09	0	0.09	0.08	1										
Lin. 2002	0	0.2	0	0.17	0.45	0	0	0	0	0.17	0	0	0.13	1									
Mar. 2016	0	0.25	0.11	0	0.36	0.3	0.22	0.22	0.11	0	0.11	0.2	0.43	0.15	1								
Pul. 2018	0	0	0	0	0.1	0	0	0	0	0	0	0	0	0.17	0	1							
Ryf. 2006	0	0.25	0	0.11	0.73	0.08	0	0	0	0.11	0	0	0.25	0.5	0.29	0.11	1						
Sut. 2023	0	0	0	0	0.07	0.25	0.14	0.33	0.17	0	0.17	0.29	0.06	0	0.15	0	0	1					
Sva. 2000	0	0.5	0.11	0	0.19	0.08	0.1	0	0	0	0	0	0.54	0.15	0.38	0	0.2	0	1				
Tan. 2011	0	0.29	0.08	0	0.37	0.23	0.17	0.08	0.08	0	0.08	0.07	0.44	0.12	0.4	0	0.31	0.06	0.31	1			
The. 2015	0	0.33	0	0	0.2	0	0	0	0	0	0	0	0.18	0.33	0.22	0	0.22	0	0.22	0.17	1		
Woo. 2020	0	0.21	0	0.04	0.37	0.12	0.04	0.09	0.04	0.04	0.04	0.08	0.31	0.21	0.28	0.04	0.39	0.07	0.23	0.3	0.09	1	
Zil. 2015	0	0.18	0	0.05	0.43	0.14	0.05	0.1	0.05	0.05	0.05	0.1	0.29	0.24	0.32	0.05	0.45	0.08	0.21	0.33	0.1	0.79	0
	0.01	**0.14**	**0.05**	**0.02**	**0.19**	**0.17**	**0.16**	**0.16**	**0.12**	**0.02**	**0.1**	**0.13**	**0.18**	**0.14**	**0.2**	**0.02**	**0.18**	**0.08**	**0.15**	**0.18**	**0.09**	**0.17**	**0.18**

Note. Each study is denoted by mentioning the first three letters of the first author, alongside with the year of publication. The line in bold represents the correlation (columnwise) with the measures in that paper with the remaining measurements across the other twenty-two papers.

Figure 2

Visualization of AL biomarker overlap across the 23 studies identified in the literature survey



Note. Co-occurrence of 38 AL biomarkers across 23 studies. Biomarker abbreviations: aSBP: aortic systolic blood pressure, BF: body fat, BMI: body mass index, BP: blood pressure, Cat: catecholamines, Chol: cholesterol, Cort: cortisol, CRP: c-reactive protein, Cys-C: cystatin c, DHEA-S: dehydroepiandrosterone-sulfate, DBP: diastolic blood pressure, E: epinephrine, Fib: fibrinogen, Gluc: glucose, HbA1c: glycosylated hemoglobin, HDL: high density lipoprotein cholesterol, HSP: high frequency spectral power, IR: insulin resistance, HR: heart rate, ICAM-1: intracellular adhesion molecule-1, IL-1β: interleukin 1β, IL-1ra: interleukin-1 receptor antagonist, IL-6: interleukin-6, IL-10: interleukin-10, LDL: low density lipoprotein cholesterol, LSP: low-frequency spectral power, MMP-9: matrix metalloproteinase-9, NE: norepinephrine, pSBP: peripheral systolic blood pressure, pDBP: peripheral diastolic blood pressure, RMSSD: root mean square of successive differences, SBP: systolic blood pressure, SDRR: heart rate variability - standard deviation of R-R intervals, sE-S: sE-Selectin, sICAM-1: soluble intercellular adhesion molecule-1, sIL-6R: soluble IL-6 receptors, sTNFR1: soluble tumor necrosis factor receptor 1, TGFβ-1: transforming growth factor beta 1, Tot/HDL: total cholesterol to high density lipoprotein cholesterol ratio, Trig: triglycerides, We: weight, WC: waist circumference, W/H: waist-to-hip ratio. Colored circles for an AL biomarker indicate that this pertains to a primary mediator, while empty circles refer to a secondary mediator

Methods of measurement. In this section, the consistency of measurement methods for the five most studied AL biomarkers (CRP, IL-6, HDL, SBP and DBP) will be evaluated. In Table 2, all measurement methods for the 38 assessed AL biomarkers for every included study are described. Overall, most studies were consistent in their chosen measurement methods for the AL biomarkers. For example, most studies measuring CRP and/or IL-6 opted for a method where they collected dried blood spots on filter cards. Additionally, studies consistently required participants to fast before HDL data collection and measured blood pressure using non-invasive methods, avoiding any skin penetration or instrument insertion.

However, specific details of the measurement process varied, such as the amount of collected dried blood spots during data collection. Furthermore, varying instruments were used across studies to collect data on the AL biomarkers. For instance, six different instruments were used across studies assessing CRP and IL-6. Moreover, blood pressure was measured at various body locations; some studies opted for the arms, while others chose the finger or aortic trunk, with participants inconsistently instructed to sit or lie down. In summary, the measurement methods for AL biomarkers were generally consistent, although there was less consensus regarding specific details of the measurement process.

PIL-AL relationship

Cross-sectional studies

Significance. Among the 14 cross-sectional studies, 68 statistical tests were performed to investigate the relationship between PIL, MIL or SOC and AL biomarkers. These tests comprised 32 correlation analyses, 30 regression analyses and 6 ANOVA analyses. Nine statistical tests from four distinct studies (Davis et al., 2015; Lindfors & Lundberg, 2002; Pulopulos et al., 2018; Ryff et al., 2006) investigated PIL's relationship with primary AL biomarkers (cortisol, DHEA-s, epinephrine and norepinephrine). The remaining

58 statistical tests from 11 distinct studies (Berkowitz et al., 2023; Campos-Uscanga et al., 2022; Friedman et al., 2007; Gouin et al., 2017; Ironson et al., 2018; Lee et al., 2022; Marteinsdottir et al., 2016; Ryff et al., 2006; Svartvik et al., 2000; Tanaka et al., 2011; Thege et al., 2015) investigated PIL's relationship with secondary AL biomarkers (e.g., SBP, DBP and cholesterol). In total, 22 of the 68 (32.35%) performed statistical tests resulted in statistically significant relationships between PIL, MIL or SOC and AL biomarkers. The specific estimates are available in Table S3. Regarding primary AL biomarkers, nine statistical tests were performed across four studies, among which three studies identified statistically significant relationships between PIL, MIL or SOC and norepinephrine and cortisol (Davis et al., 2015; Lindfors & Lundberg, 2002; Ryff et al., 2006). Regarding secondary AL biomarkers, 59 statistical tests were performed across 11 distinct studies, among which eight studies identified statistically significant relationships between PIL, MIL or SOC and SBP, DBP, HDL, Tot/HDL, triglycerides, W/H, weight, BMI, HbA1c, WC, IL-6, MMP-9, sIL-6R and IL-1β (Berkowitz et al., 2023; Friedman et al., 2007; Gouin et al., 2017; Lee et al., 2022; Marteinsdottir et al., 2016; Ryff et al., 2006; Svartvik et al., 2000; Tanaka et al., 2011). None of the included cross-sectional studies measuring aSBP, pSBP, BP, pDBP, LDL, BF, HbA1c, glucose, IR, CRP, morning cortisol, DHEA-S and E found statistically significant relationships with PIL. Additionally, one cross-sectional study examined the relationship between SOC and AL as a unitary variable that consisted of multiple AL biomarkers (Tanaka et al., 2011), which appeared insignificant.

Direction. Most cross-sectional studies investigated the PIL-AL relationship with AL (biomarkers) considered as the dependent variable and PIL, MIL or SOC as (the) independent variable(s). In contrast, one study treated SOC as a dependent variable (Svartvik et al., 2000). However, in line with the approach taken by the authors from the other studies, Svartvik and colleagues argued that a high SOC would lead to improved health, meaning that all studies

reasoned that PIL, MIL or SOC impact health outcomes rather than the other way around. Among the 22 statistical tests that showed statistically significant relationships between PIL and AL biomarkers, 14 (63.64%) pointed to a negative relationship, while eight (36.36%) indicated a positive relationship.

Regarding primary AL biomarkers, Lindfors and Lundberg (2002) found that PIL was negatively related to cortisol, whereas Ryff et al. (2006) found that PIL was positively related to cortisol. Additionally, Davis et al. (2015) found that PIL was negatively associated with norepinephrine. Regarding secondary AL biomarkers, SOC was positively related to SBP and DBP in two studies (Svartvik et al. 2000; Tanaka et al. 2011) and to HDL in one study (Svartvik et al. 2000) and PIL (Ryff et al. (2006). SOC was negatively related to Tot/HDL in one study (Tanaka et al. 2011), as well as triglycerides (Svartvik et al. 2000). SOC was positively related to weight in one study (Svartvik et al. 2000). SOC negatively predicted BMI levels in the study by Marteinsdottir et al. (2016), although Svartvik et al. (2000) found that SOC positively predicted BMI levels. One study found that SOC negatively predicted MMP-9 (Marteinsdottir et al, 2016). PIL was negatively related to W/H in one study (Ryff et al. 2006). PIL negatively predicted WC levels in one study (Berkowit et al. 2023), but only in one of their samples. MIL negatively predicted IL-6 in one study (Gouin et al., 2017) and PIL negatively predicted IL-6 in one study (Lee et al., 2022). Lastly, PIL negatively predicted sIL-6R (Friedman et al., 2007) and IL-1β levels (Lee et al., 2022).

Effect size. When examining all significant relationships identified by cross-sectional studies, each could be classified according to the strength of the discovered relationship. Based on Cohen (1988), small relationships have a coefficient ranging between 0.10-0.30, medium relationships between 0.30-0.50 and strong relationships above 0.50. Among the 22 statistical tests that showed statistically significant relationships between PIL and AL biomarkers, 13 (59.09%) were deemed small, while three (13.64%) fell into the

medium-sized range and six (27.27%) could be considered large. Among primary AL biomarkers, all identified significant relationships were small-sized, except for one found by Lindfors and Lundberg (2002) regarding the relationship between PIL and cortisol. Among secondary AL biomarkers, small effect-sizes were found for the relationship with SBP, DBP, HDL, triglycerides, W/H, weight, IL-6 and sIL-6R, medium effect-sizes were found for the relationship with pDBP, Tot/HDL and cortisol and large effect-sizes were found for the relationship with HDL, BMI, IL-6 and IL-1β. In sum, most identified PIL-AL relationships were small-sized, although some studies also identified medium-sized and large relationships.

Longitudinal studies

Significance. Among the nine longitudinal studies, 35 statistical tests were performed to investigate the relationship between PIL, MIL or SOC and AL biomarkers. These tests comprised 16 correlation analyses, 18 regression analyses and one survival analysis. Importantly, all correlation analyses were done to investigate the relationship between PIL and AL biomarkers cross-sectionally. Therefore, in order to distinguish between cross-sectional and longitudinal relationships, the results of these statistical tests will be discussed separately. Cross-sectionally, 7 of the 16 (43.75%) performed statistical tests resulted in statistically significant relationships between PIL, MIL or SOC and AL biomarkers. One study (Zilioli et al., 2015) executed two statistical tests to investigate PIL's relationship with primary AL biomarkers (cortisol, DHEA-S, epinephrine and norepinephrine), which both appeared insignificant. The specific estimates can be retrieved in Table S4. Also, 14 statistical tests were done by four distinct studies (Boylan & Ryff, 2015; Friedman & Ryff, 2012; Giannis et al., 2023; Zilioli et al., 2015) to investigate PIL's relationship to secondary AL biomarkers. Among those, statistically significant relationships were identified between PIL and triglycerides, HDL, WC, W/H, BMI, sE-S and RMSSD

(Boylan & Ryff, 2015; Friedman & Ryff, 2012; Giannis et al., 2023; Zilioli et al., 2015). No statistically significant relationships with PIL were found for SBP, DBP and glucose. Longitudinally, 8 of the 19 (42.11%) performed statistical tests resulted in statistically significant relationships between PIL, MIL or SOC and AL biomarkers. One study (Hsiao et al., 2014) executed four statistical tests to investigate PIL's relationship with cortisol as an AL biomarker 8 months later, which all appeared insignificant. Also, ten statistical tests were done by four distinct studies (Friedman & Ryff, 2012; Giannis et al., 2023; Guimond et al., 2022; Sutin et al., 2023) to investigate PIL's relationship with secondary AL biomarkers. Among those, statistically significant relationships were identified by two studies between PIL and CRP, IL-6, IL-1ra, IL-10 and sTNFR1 (Friedman & Ryff, 2012; Sutin et al., 2023). No statistically significant relationships with PIL were found for TGFβ-1. Additionally, five statistical tests were done by four studies to examine the relationship between PIL and a unitary variable that consisted of multiple AL biomarkers (AL and MSC; Boylan & Ryff, 2015; Lewis & Hill, 2023; Woo et al., 2020; Zilioli et al., 2015). Among those, two studies showed that PIL significantly predicted variations in MSC 9-10 years later (Boylan & Ryff, 2015) and AL ten years later (Zilioli et al., 2015). Also, Zilioli et al. (2015) assessed whether PIL was related to several subgroups of AL biomarkers and found that PIL was significantly correlated to metabolic lipids (incl. BMI, W/H, triglycerides, HDL and LDL), inflammation variables (incl. IL-6, CRP, fibrinogens, sE-S and sICAM-1) and parasympathetic nervous system variables (incl. SDRR, RMDSSD and low and high frequency spectral power), but not to cardiovascular variables (incl. SBP, DBP and HR), glucose metabolism variables (HbA1c, glucose and IR), sympathetic nervous system variables (epinephrine and norepinephrine) and hypothalamic pituitary adrenal axis variables (incl. cortisol and DHEA-S).

Direction. All nine longitudinal studies investigated the PIL-AL relationship with PIL considered as the independent variable and AL (biomarkers) as the dependent variable(s).

Among the 16 statistical tests that showed statistically significant relationships between PIL and AL biomarkers, 14 (87.50%) pointed to a negative relationship, while two (12.50%) indicated a positive relationship. Cross-sectionally, two studies found that PIL was negatively related to BMI (Giannis et al., 2023; Zilioli et al., 2015), one study found that PIL was negatively related to W/H (Friedman & Ryff, 2012), triglycerides and WC (Boylan & Ryff, 2015) and sE-S and RMSSD (Zilioli et al., 2015). Longitudinally, PIL positively predicted CRP levels in the study of Friedman et al. (2012), whereas Sutin et al. (2023) found that PIL negatively predicted CRP levels 2-4 years later. Also, Sutin et al. (2023) found that PIL negatively predicted IL-6, IL-1ra, IL-10 and sTNFR1 levels 2-4 years later. Boylan & Ryff (2015) found that PIL positively predicted HDL levels 9-10 years later. Considering PIL's potential in predicting the levels of unitary variables that consisted of multiple AL biomarkers, Boylan & Ryff (2015) found that PIL negatively predicted MSC levels 9-10 years later and Zilioli et al. (2015) found that PIL negatively predicted AL levels ten years later.

Effect-size. The results of all 16 statistical tests that showed statistically significant relationships between PIL and AL biomarkers were deemed small-sized.

Mediating effects

Mediators within the PIL-AL relationship

Two studies have delved into mediators within the PIL-AL relationship. Berkowitz et al. (2023) explored cross-sectionally whether healthier eating habits explained why PIL was related to smaller waist circumference (WC) in American (MIDUS cohort) and Chilean (CHILDEMED cohort) populations. They found that PIL was indirectly related to lower WC through healthier eating habits in both cohorts. This indicates that PIL might lead to lower

AL rates by encouraging better dietary choices, although this study only assessed one AL biomarker.

Moreover, Zilioli et al. (2015) conducted a longitudinal study to examine whether one's SOC over their life mediated the PIL-AL relationship. Their findings suggested that PIL was indirectly associated with AL via more ILOC. This implies that having a stronger PIL might lead to lower AL rates by fostering a sense of personal control over one's life, which promotes healthier behaviors. However, it was found that fostering a sense of external control did not explain why having a weaker PIL leads to higher AL rates. Moreover, AL biomarkers were only measured after a 10-year follow-up, so it could not be ruled out that the relationship was present at baseline. Furthermore, causality could not be established since the mediators were assessed simultaneously with AL. Thus, having a strong ILOC could explain the PIL-AL relationship, but the study's limitations should be considered. In conclusion, there are definitive indications that a stronger PIL might lead to lower AL rates by encouraging healthier behaviors, both in terms of eating habits and broader lifestyle choices.

AL biomarkers as mediators

Two longitudinal studies also examined the mediating role of AL biomarkers in relation to PIL. For example, Sutin et al. (2023) investigated whether inflammation levels explained why individuals with a stronger PIL are in better cognitive health, measured by episodic memory (EM). Results confirmed that more PIL was associated with better EM, partly through healthier levels of IL-6, but not through CRP, IL-10 or IL-1ra. However, IL-6 accounted for only 4.50% of the PIL-EM relationship.

Also, Woo et al. (2020) investigated whether AL partly mediated the negative relationship between PIL and chronic conditions 7-10 years later. Data were derived from the MIDUS study and included a subsample of 850 individuals aged 34-83 who participated in

the MIDUS 2 survey, the Biomarker Project (the fourth MIDUS project aiming to investigate the role of behavioral, psychological, and social factors in understanding age-related differences in physical and mental health) and the MIDUS 3 survey. Results showed that AL did not mediate the relationship between psychological resources, including PIL, and chronic conditions. This null finding was due to the finding that psychological resources were not associated with AL. In conclusion, it was found that IL-6, but not CRP or IL-1ra, partly explained why purposeful individuals are cognitively healthier, and that participants with more psychological resources did not have lower AL.

Moderating effects

Moderators within the PIL-AL relationship

Age. Several studies examined how age influenced the PIL-AL relationship. To start, Lee et al. (2022) found that older adults (aged 60+) with a stronger PIL had lower inflammation levels, including IL-1β and IL-6, while this relationship was insignificant in younger adults (aged 18-35). This suggests that PIL may protect against inflammation in older age, but not in younger age. Giannis et al. (2023) examined whether age moderated the relationship between PIL and CRP levels. Results showed that increasing PIL over time was associated with reduced inflammation in early old age (73 years) but not in advanced old age (81 years). Also, the findings showed that age explained 14.30% of the variance in the relationship between changes in PIL and CRP, above and beyond the included covariates. This implies that the benefits of PIL on inflammation might diminish as people get older. Guimond et al. (2022) tested whether the relationship between PIL and CRP levels changed for participants aged <75 years compared to those aged >75 years, but their results did not show a significant interaction effect.

Additionally, all 23 studies were compared based on whether their sample primarily consisted of younger or older adults to investigate the potential moderating role of age within the PIL-AL relationship. In total, 16 of the 23 included studies had a mean age below 65 years old (Berkowitz et al., 2023; Boylan & Ryff, 2015; Campos-Uscanga et al., 2022; Davis et al., 2015; Friedman & Ryff, 2012; Gouin et al., 2017; Hsiao et al., 2014; Lee et al., 2022; Lindfors & Lundberg, 2002; Marteinsdottir et al, 2016; Pulopulos et al., 2018; Svartvik et al., 2000; Tanaka et al., 2011; Thege et al., 2015; Woo et al., 2020; Zilioli et al., 2015) and seven above 65 years old (Friedman et al., 2007; Giannis et al., 2023; Guimond et al., 2022; Ironson et al., 2018; Lewis & Hill, 2023; Ryff et al., 2006; Sutin et al., 2023). Among the 16 studies primarily examining younger adults, 78 statistical tests were performed to assess the PIL-AL relationship, among which 27 (34.61%) were deemed statistically significant. Among the seven studies primarily investigating older adults, 24 statistical tests were performed to examine the PIL-AL relationship, among which ten (41.67%) appeared significant. Thus, the PIL-AL relationship was more present when primarily older adults were included in the sample. In sum, two out of three studies investigating age as a moderator of PIL-AL found a significant relationship, but their findings were contradicting, and among all included studies, more significant PIL-AL relationships were found when primarily older adults were included in the sample.

Sex. One study, done by Guimond et al. (2022) investigated the potential moderating effect of sex. They investigated whether sex moderated the relationship between PIL and CRP levels, but found no statistically significant moderating effect of sex ($p=.15$). However, they observed that the relationship between PIL and CRP was stronger in men than in women. To illustrate, men with the strongest PIL had a 29% lower risk of developing unhealthy CRP levels compared to those with the weakest PIL, although for women with the

strongest PIL, the risk for developing unhealthy CRP levels was not diminished. Thus, based on these findings, the PIL-AL relationship might be stronger among men than women.

Also, all 23 studies were compared based on whether their sample primarily consisted of men or women to investigate the potential moderating effect of age within the PIL-AL relationship. In total, women were primarily investigated in 19 studies (Berkowitz et al., 2023; Boylan & Ryff, 2015; Campos-Uscanga et al., 2022; Davis et al., 2015; Friedman et al., 2007; Friedman & Ryff, 2012; Giannis et al., 2023; Gouin et al., 2017; Guimond et al., 2022; Ironson et al., 2018; Lewis & Hill, 2023; Marteinsdottir et al., 2016; Pulopulos et al., 2018; Ryff et al., 2006; Sutin et al., 2023; Svartvik et al., 2000; Thege et al., 2015; Woo et al., 2020; Zilioli et al., 2015), while men were mostly investigated in three studies (Lee et al., 2022; Lindfors & Lundberg, 2002; Tanaka et al, 2011). Among the studies primarily investigating women, 32 out of 84 (38.10%) PIL-AL relationships appeared significant, whereas, among the studies predominantly examining men, five out of 18 (27.78%) PIL-AL relationships appeared significant. Thus, in proportion, more statistically significant PIL-AL relationships were found when women were predominantly investigated. In sum, one study proposed that possessing a high PIL is related to diminished inflammation levels in men, but not in women, although statistical evidence was lacking, but the studies within this review found more significant PIL-AL relationships when women dominated the sample.

PIL as a moderator

Several studies investigated the moderating role of PIL. First, Friedman & Ryff (2012) investigated whether PIL moderated the relationship between number of chronic conditions and IL-6 and CRP. The number of chronic conditions reflected the extent to which participants had received a diagnosis for any of 12 chronic conditions (e.g., autoimmune disorders, cardiovascular and cerebrovascular diseases or hypertension). Results showed that,

after covariate adjustment, the interaction effect was significant for IL-6 (β=-.36, $p<.05$) and CRP (β=-.36, $p<.05$). This implies that, although inflammation levels increased with an increasing number of chronic conditions, participants with higher PIL levels still had lower inflammation levels compared to those with lower PIL levels. However, the interaction effects explained only 1-2% of the variance in inflammation levels. In short, PIL slightly diminished the impact of chronic conditions on inflammation levels.

Secondly, Gouin et al. (2017) investigated whether meaningful engagement (ME) moderated the impact of adverse childhood experiences (ACE; e.g., sexual abuse and emotional or physical neglect) among individuals with elevated IL-6 and CRP levels. Results showed that ME interacted with ACE to predict IL-6, but not CRP. This indicated that, among participants with more ACE, those with greater ME, had lower IL-6 levels compared to those with less ME. In short, ME attenuated the impact of ACE on IL-6, but not on CRP.

Thirdly, Pulopulos et al. (2018) delved into the moderating role of MIL in the relationship between perceived stress and cortisol. MIL was divided in value-related MIL - the perception that life activities are valuable and important - and directedness-related MIL - the possession of goals and a sense of excitement about one's future. Cortisol was measured as cortisol DCS, the decrease in cortisol secretion from morning to evening, and cortisol AUCg, the overall diurnal cortisol secretion. Results showed that value-related MIL, but not directedness-related MIL, significantly moderated the relationship between perception of stress and cortisol DCS and AUCg. Specifically, a higher perception of stress was related to higher cortisol DCS/AUCg in people with low levels of value-related MIL, but this relationship disappeared in people with medium or high levels of value-related MIL. In short, more value-related ML protected stressful individuals against high cortisol levels, but directedness-related ML did not. In conclusion, PIL slightly weakened the impact of chronic conditions on inflammation levels, ME mitigated the impact of ACE on IL-6 levels, but not

on CRP, and value-related MIL, but not directedness-related MIL, lessened the impact of perceived stress on cortisol.

Causality

Although none of the 23 included studies used experimental designs, nine used longitudinal designs with follow-up periods ranging from eight months to 12 years. Although longitudinal studies cannot directly establish causality without experimental manipulation, they provide stronger evidence under certain conditions. For instance, all theoretical covariates must be included (Antonakis et al., 2010) and the sample must be representative of the target population (Andrade, 2018). Also, both PIL and AL should be assessed at all study waves to ensure that the relationship was not present at baseline (Taris & Kompier, 2014).

Firstly, some studies could not draw causal conclusions because they found that PIL and AL (biomarkers) were unrelated. For example, Giannis et al., (2023) found that PIL did not significantly predict CRP between-persons and changes in PIL within-persons did not predict changes in CRP six years later. Also, Friedman & Ryff (2012) found that PIL did not significantly predict inflammation markers 8-11 years later. Notably, studies involving MIDUS data showed that PIL predicted AL ten years later, but PIL did not predict AL cross-sectionally (Zilioli et al., 2015; Boylan & Ryff, 2015).

Secondly, regarding the criterium that PIL and AL should be measured at every study wave, AL biomarker data was not measured at baseline in studies involving HRS data (Sutin et al., 2023; Guimond et al., 2023) and MIDUS data (Zilioli et al., 2015; Woo et al., 2020; Boylan & Ryff, 2015; Friedman & Ryff, 2012). Also, in the ELSA study, PIL was assessed at baseline, but not at follow-up (Lewis & Hill, 2023).

Thirdly, unrepresentative samples posed challenges for making causal claims. For example, in the study of Hsiao and colleagues (2014), the MIL and cortisol patterns remained

stable throughout the study period and suggested low levels of psychological stress. This was unusual given that the target population of the study involved breast cancer survivors, who usually exhibit high stress levels. Likely, these atypical stress patterns stemmed from the studies' exclusion criteria, as patients with severe cancer types were excluded. Moreover, the limited response rate (18%) further weakened the representativeness of the sample. Besides this, the HRS sample was not representative of the target population because it involved a select group of U.S. participants (Sutin et al., 2023; Guimond et al., 2023) and the MIDUS sample included a limited number of individuals from racial and ethnic minority groups (Zilioli et al., 2015; Woo et al., 2020; Boylan & Ryff, 2015; Friedman & Ryff, 2012).

Lastly, PIL-AL relationships disappeared when controlled for health covariates (Friedman & Ryff, 2012), negative affect (Friedman & Ryff, 2012), sociodemographic covariates (Guimond et al., 2023) or depressive symptoms (Lewis & Hill, 2023). Also, studies did not always include all impactful covariates (e.g., gratitude and optimism), which further complicated inferring a causal relationship (Giannis et al., 2023). Overall, none of the included longitudinal studies established robust causal claims due to a lack of significant longitudinal relationships (after controlling for covariates), unconsidered covariates, absence of baseline/follow-up measurements, unrepresentative samples or insufficient power.

Discussion

This SLR investigated the PIL-AL relationship, with the aim of informing future research on PIL's potential in mitigating AL. The results of 23 studies were analyzed, including 14 cross-sectional and nine longitudinal studies. Across the studies, PIL, MIL or SOC were assessed in relation to 38 different AL biomarkers, including four primary and 34 secondary AL biomarkers. Overall, the results of 103 statistical tests resulted in 38 (36.27%) statistically significant relationships between PIL and AL biomarkers. This partly supports

the original hypothesis stating that PIL would be significantly related to AL (Burrow et al., 2024; Lindfors et al., 2006; Shojaee & French, 2014; Suvarna et al., 2020). Among the statistically significant PIL-AL relationships, most were negative, which is in line with the original hypothesis stating that more PIL was related to less AL (Burrow et al., 2024; Lindfors et al., 2006; Shojaee & French, 2014; Suvarna et al., 2020). Also, most significant relationships were small-sized, meaning that PIL and AL were only marginally related, if at all. A possible explanation for the insignificant findings is that PIL also increases, instead of diminishes, AL biomarker rates. To illustrate, Baumeister et al. (2013) found that individuals with higher MIL had more stress, likely due to their heightened engagement in stressful activities, like dwelling on past and future experiences. Future research should point out whether engagement in stressful activities moderates the PIL-AL relationship.

Additionally, PIL, MIL or SOC related differently to individual AL biomarkers. To illustrate, negative relationships were consistently found between PIL, MIL or SOC and norepinephrine, the cholesterol to HDL ratio, triglycerides, MMP-9, waist-to-hip ratio, waist circumference, IL-6, sIL-6R and IL-1β (Davis et al., 2015; Tanaka et al., 2011, Svartvik et al., 2000; Marteinsdottir et al., 2016; Ryff et al., 2006; Berkowitz et al., 2023; Gouin et al., 2017; Lee et al., 2022; Friedman et al., 2007). In contrast, positive relationships were consistently found between SOC and SBP, DBP and weight (Svartvik et al., 2000; Tanaka et al., 2011). On top of this, Zilioli et al. (2015) divided AL into several subgroups and found that PIL was significantly related to some subgroups of AL biomarkers, but not to others. Regarding blood pressure, Svartvik and colleagues (2000) proposed that individuals with lower SOC exhibited reduced blood pressure levels due to a less active lifestyle. Likewise, individuals suffering from depression and anxiety had lower blood pressure levels 11 years later (Hildrum et al., 2008). Besides inconsistencies regarding the direction of the PIL-AL relationship, differences in effect-size were observed. For instance, small effect-sizes were consistently found for

PIL's relationship with blood pressure and waist-to-hip ratio (Friedman & Ryff, 2012; Svartvik et al., 2000; Ryff et al., 2006), whereas larger effect-sizes were found for PIL's relationship with HDL and BMI (Marteinsdottir et al., 2016; Svartvik et al., 2000). These inconsistencies bring the use of AL as a unitary construct into question. Future research should determine whether the five most impactful AL biomarkers, as identified by McCrory and colleagues (2023), should be combined into a unitary construct or analyzed separately due to their different relationships with PIL.

Besides this, some studies contradicted each other not only regarding the relationship between PIL and various biomarkers, but also with respect to the same biomarkers. For example, five studies identified null results regarding the relationship between PIL, MIL or SOC and SBP (Boylan & Ryff, 2015; Zilioli et al., 2015; Marteinsdottir et al., 2016; Ryff et al., 2006; Thege et al., 2015), except for Svartvik and colleagues (2000), who found that SOC had a significant positive relationship with SBP. A possible explanation is that Svartvik and colleagues (2000) measured SBP while participants were lying down, whereas the other studies measured SBP while patients were sitting. In agreement with this, Bartling and colleagues (2020) showed that changing posture from lying to sitting causes an increase in blood pressure levels in a normal human population. Furthermore, Lee and colleagues (2022) found that PIL and CRP were unrelated, whereas PIL and CRP were significantly related in the studies done by Friedman and colleagues (2012) and Sutin and colleagues (2023). Notably, Lee and colleagues (2022) measured CRP by obtaining saliva samples, whereas the other studies opted for the dried blood method. Goetz and Lucas (2020) discovered that CRP levels obtained from dried blood spots and saliva were not significantly related in healthy African-Americans. Moreover, saliva CRP levels display diurnal variations (Izawa et al., 2013), whereas blood CRP levels remain stale (Mills et al., 2009). Thus, slight variations in measurement methods of the AL biomarkers potentially caused inconsistencies in the results.

Moreover, results from the Jaccard Index showed that the overall similarity correlation was very weak (Figure 2), meaning that the studies examined a varied set of AL biomarkers with little overlap, which further complicated comparing the results. Therefore, future studies should find consensus regarding the measurement methods of AL biomarkers and focus primarily on the AL biomarkers most predictive of health outcomes (McCrory et al., 2023).

Regarding moderating effects, three studies found inconsistent results regarding the moderating role of age within the PIL-AL relationship, with one study finding that the PIL-AL relationship disappeared with increasing age (Giannis et al., 2023), one study finding that the PIL-AL relationship disappeared with diminishing age (Lee et al., 2022) and one study finding null results (Guimond et al., 2022). Thus, the results of one study were in line with the original hypothesis stating that the PIL-AL relationship weakens as individuals age. Possibly, it is more challenging for older adults to alleviate their increased AL rates given their decreased PIL levels (Calder et al., 2017; Mackenzie et al., 2018; Ryff, 1989; Springer et al., 2011). Likewise, Giannis and colleagues (2023) reasoned that older adults struggle to achieve their goals, meaning that having a PIL might not protect them from health consequences anymore (Wrosch et al., 2007). Pinquart (2002) adds that declining health, often experienced in older adulthood, affects PIL by impeding goal engagement. However, in proportion, more statistically significant PIL-AL relationships were identified when the sample primarily consisted of older adults (41.70%), compared to those primarily investigating younger adults (34.60%). This temptingly indicated that the PIL-AL relationship is weaker among younger adults, which contrasts the original hypothesis. Potentially, younger adults with more PIL face more difficulties due to heightened life expectations, which burdens their health (Lee et al., 2022). However, older adults were underrepresented among the included studies, which means the results should be interpreted

carefully. Future studies investigating the moderating effect of age are needed to clarify the origins of these contradictory findings.

Besides this, the moderating role of sex was investigated by comparing studies examining primarily women to those primarily investigating men. The results showed that, in proportion, more statistically significant PIL-AL relationships (38.10%) were identified when the sample primarily consisted of women compared to those primarily investigating men (27.80%). This finding is in line with the original hypothesis, stating that the PIL-AL relationship would be stronger for women, as this was the case for the relationship between positive affect and AL (Schenk et al., 2018). However, these results should be interpreted carefully since men were underrepresented in the included studies. Moreover, one of the included studies did not find a statistically significant interaction effect of sex (Guimond et al., 2022), which contrasts the original hypothesis.

Next, the moderating role of clinical status was investigated. In total, two studies primarily investigated clinical individuals, with one focusing on individuals who received a diagnosis for any of 12 chronic conditions (e.g., autoimmune disorders, cardiovascular and cerebrovascular diseases or hypertension) and one including patients with epithelial ovarian cancer. Both studies found that PIL had a beneficial impact on patients' AL biomarker levels, despite their illnesses (Friedman & Ryff, 2012; Davis et al., 2015). These findings temptingly indicate that individuals suffering from diseases still benefit from an elevated PIL level. This contrasts the original hypothesis, stating that the PIL-AL relationship disappears among patients due to their reduced PIL levels (Boreham & Schutte, 2023) and elevated AL rates (Honkalampi et al., 2021). However, none of the studies investigated the moderating role of clinical status directly, meaning that more studies are needed to point out whether the PIL-AL relationship changes among clinical and non-clinical individuals.

Also, two studies assessed mediating factors within the PIL-AL relationship. The findings of both studies suggested that PIL/SOC might lead to lower AL rates by fostering a stronger sense of control over one's life, which encourages healthy-promoting behaviors (Berkowitz et al., 2023; Zilioli et al., 2015). These findings are in agreement with research indicating that purposeful individuals exhibit a higher ILOC (Shojaee & French, 2014), which correlates with the adoption of healthier behaviors, and consequently, lower AL rates (Suvarna et al., 2020). Furthermore, Kim et al. (2020) found that individuals with the highest PIL had a 15% increased likelihood of engaging in frequent physical activity and a 13% reduced risk of sleeping problems compared to those with the lowest PIL. However, the findings of both studies should be considered carefully since baseline measurements for AL biomarkers were absent (Berkowitz et al., 2023; Zilioli et al., 2015). Future studies under appropriate methodological conditions are needed to establish the mediating role of ILOC to confirm that purposeful individuals have lower AL rates because they make healthier choices.

Additionally, none of the included longitudinal studies established causal claims, mainly due to the absence of experimental manipulation. Therefore, it could not be ruled out that the variation from AL rates from baseline to follow-up was caused by something else than variations in PIL. Other prominent factors hindering making causal claims were a lack of significant PIL-AL relationships (after covariate adjustment) and methodological weaknesses, such as unrepresentative samples (Boylan & Ryff, 2015; Friedman & Ryff, 2012; Giannis et al., 2023; Guimond et al., 2022; Hsiao et al., 2014; Sutin et al., 2023; Woo et al., 2020; Zilioli et al., 2015), absence of baseline or follow-up measurements (Boylan & Ryff, 2015; Friedman & Ryff, 2012; Sutin et al., 2023; Woo et al., 2020; Zilioli et al., 2015) and unconsidered covariates (Giannis et al., 2023; Lewis & Hill, 2023). Notably, studies including the MIDUS sample observed that PIL predicted AL rates longitudinally, but not cross-sectionally (Boylan & Ryff, 2015; Zilioli et al., 2015). The authors reasoned that the

impact from PIL on AL may come gradually over time. Likewise, connecting PIL to AL at one point in time might not be desirable because PIL guides daily choices more like a compass than a controlling force (McKnight & Kashdan, 2009), indicating that having a PIL does not mean that individuals always adhere to it. However, while taking all included longitudinal studies into consideration, an equal ratio of significant PIL-AL relationships was found when both constructs were measured either cross-sectionally (43.75%) or longitudinally (42.11%). To ensure whether the impact of PIL on AL changes over time, experimental studies with representative samples and sufficient power, that control for as many relevant covariates as possible, are needed.

Finally, the NOS was used to assess the studies' quality. In total, one study was deemed low quality, most were average quality and some were high quality. The main reasons for compromised study quality were unrepresentative samples and a lack of information on non-respondents. Specifically for longitudinal studies, more than half of the studies did not measure PIL and AL at every study wave and/or had an unrepresentative or small sample. The follow-up period mostly had a sufficient duration. Thus, most studies received an average quality score, but future studies should acquire extensive representative samples, report on non-respondents and measure constructs at all study waves.

While interpreting the findings of this review, its strengths and limitations should be considered. First, numerous studies merely mentioned terms such as "allostasis" and "allostatic overload" (Christensen et al., 2022; Finlay et al., 2022; Guidi et al., 2020), whereas this review adopted a more comprehensive approach by also incorporating specific primary and secondary AL biomarker names into the search string. Also, MIL and SOC were included as similar to PIL, which also reduced the risk of overlooking relevant articles. However, some articles may still have been overlooked due to the absence of keywords such as "life significance" (Martela & Steger, 2016), "dopamine", "aldosterone", "waist-to-height ratio",

"homocysteine", etc. (Juster et al., 2010). Moreover, this thorough search potentially diminished the reliability of the comparison of results across studies as PIL, MIL and SOC are intercorrelated yet distinct concepts according to Martela & Steger (2016). Occasionally, this made it difficult to determine whether contrasting findings were due to PIL having different relationships with individual AL biomarkers, or if PIL, MIL, or SOC relate differently to AL in general. Also, the fact that studies assessing single biomarkers were considered may also be viewed as a limitation, as relying on one single biomarker to quantity stress may be unrealistic (Kokka et al., 2023).

In conclusion, this review consolidated and analyzed findings regarding the PIL-AL relationship from 23 studies. The results provided limited evidence for a PIL-AL relationship since mostly null results or small-sized relationships were identified. Most significant PIL-AL relationships were negative, as expected from prior research on the relationship between PIL and subjective stress (Sutin et al., 2024). Notably, the results showed considerable variation for PIL's relationship with individual AL biomarkers, which questions the usage of AL as a unitary concept. Also, studies showed heterogeneity regarding AL biomarker inclusion and measurement methods. Therefore, future studies should find consensus and apply standardized procedures. Few studies investigated moderators or mediators, which highlighted the need for further exploration of such factors. Most results conflicted regarding the moderating role of age and sex, but an enhanced adoption of health-promoting behaviors consistently mediated the PIL-AL relationship. Since none of the study-designs were suitable for establishing causality, future studies should prioritize (quasi-) experimental designs. Studies were average quality, but methodological improvements, such as representative sampling, adequate power, baseline and follow-up measurements, and covariate inclusion, are essential in the future. In short, this review provided limited evidence for a PIL-AL relationship, and offered guidance for future studies.

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Supplementary materials

S1 Table

Study Quality Assessment using the Newcastle-Ottawa Scale (NOS) for cross-sectional studies.

	Selection			Comparability	Outcome			
Study	1	2	3	4	5	6	Stars	Study quality
1 Berkowitz et al. 2023	- Unrepresentative sample	* Description of non-participants was available	* PIL subscale of the Ryff's psychological well-being questionnaire	**	* Independent blind assessment	* Student's t-test, one-way ANOVA tests, multivariate linear regression	6	High
2 Campos-Uscanga et al. 2022	- Unrepresentative sample	* Response rate was 98%	* PIL subscale of the Ryff's psychological well-being questionnaire	- No covariates	* Independent blind assessment	* Student's t-test	4	Medium
3 Davis et al. 2015	- Only women	- No information available	* PIL subscale of the Ryff's psychological well-being questionnaire	**	* Independent blind assessment	* Structural equation model (SEM)	5	Medium
4 Friedman et al. 2007	- Unrepresentative sample	* Description of non-participants was available	* PIL subscale of the Ryff's psychological well-being questionnaire	**	* Independent blind assessment	* Multivariate hierarchical regression	6	High

5 Gouin et al. 2017	- Unrepresentative sample	- No information available	* Meaningful engagement subscale of the REMAP scale	**	* Independent blind assessment	* Hierarchical linear regression analyses	5	Medium
6 Ironson et al. 2018	- Selected group	- No information available	- No validated questionnaire used	**	* Independent blind assessment	* Hierarchical regressions	4	Medium
7 Lee et al. 2022	- Unrepresentative sample	- No information available	* PIL subscale of the Ryff's psychological well-being questionnaire	**	* Independent blind assessment	* Independent t-tests, Mann-Whitney U test	5	Medium
8 Lindfors & Lundberg 2022	- Unrepresentative sample	- No information available	* PIL subscale of the Ryff's psychological well-being questionnaire	- No covariates	* Independent blind assessment	* Correlation analyses	3	Medium
9 Marteinsdottir et al. 2016	* Representative sample	- No information available	* The Orientation to Life Questionnaire	**	* Independent blind assessment	* Chi-squared tests, t-tests, linear regressions	6	High
10 Pulopulos et al. 2018	* Somewhat representative sample	- No information available	* PIL subscale of the Ryff's psychological well-being questionnaire, Life	**	* Independent blind assessment	* Correlation analyses, moderated regression analyses	6	High

			Engagement Test					
11 Ryff et al. 2006	* No information on how sample was recruited	- No information available	* PIL subscale of the Ryff's psychological well-being questionnaire	* Only medication use	* Independent blind assessment	* Correlation analyses	5	Medium
12 Svartvik et al. 2000	* Random sampling	- No information available	* The Orientation to Life Questionnaire	**	* Independent blind assessment	* Multiple regression	6	High
13 Tanaka et al. 2011	- Unrepresentative sample	- No information available	* Japanese version of SOC-13	- Only age	* Independent blind assessment	* Correlation analyses	3	Medium
14 Thege et al. 2015	- No information on how healthy sample was recruited	* Response rate was 98,5% among clinical and 92% among healthy participants	* Hungarian version of the Life Meaningful subscale from the Brief Stress and Coping Inventory, Hungarian version of the SOC-13	**	* Independent blind assessment	* Chi-square test and Mann-Whitney test	6	High

Note. *: score fulfilled, −: score not fulfilled/too little information, 1: representativeness of the sample (a * is given when the sample was truly/somewhat representative of the average population); 2: non-respondents (a * was given when comparability between respondents and non-respondents characteristics was established and/or when the response rate was satisfactory; 3: ascertainment of PIL (a * was given when PIL was measured using a validated questionnaire); 4: comparability of cohorts (a * was given when the study controlled for age and sex and an additional * was given when the study controlled for additional factors); 5: assessment of the AL (a * was given when AL biomarkers were measured via independent blind assessment/record linkage); 6: statistical test (a * was given when the statistical test used to analyze the data was clearly described and appropriate, and the measurement of the relationship was presented, including confidence intervals and the probability level (p-value)).

S2 Table

Study Quality Assessment using the Newcastle-Ottawa Scale (NOS) for longitudinal studies.

	Selection			Comparability	Outcome				
Study	1	2	3	4	5	6	7	Stars	Study quality
1 Boylan & Ryff (2015)	- Unrepresentative sample	* PIL subscale of the Ryff's psychological well-being questionnaire	- AL biomarkers were not measured at baseline	**	* Independent blind assessment	* 9-10 years	* Description of lost participants was present	6	Medium
2 Friedman & Ryff (2012)	- Unrepresentative sample	* PIL subscale of the Ryff's psychological well-being questionnaire	- AL biomarkers were not measured at baseline	**	* Independent blind assessment	* 8-11 years	* Description of lost participants was present	6	Medium
3 Giannis et al. (2023)	- Small unrepresentative sample (N=129)	* Life Engagement Test	*	*	* Independent blind assessment	* 6 years	* Description of lost participants was present	6	Medium
4 Guimond et al. (2022)	* Representative sample	* PIL subscale of the Ryff's psychological well-being questionnaire	*	**	* Independent blind assessment	* 8 years	* Response rate was between 59,1-74% but missing values were imputed	8	High

5 Hsiao et al. (2014)	- Small unrepresentative sample (N=68)	* Meaning in Life Questionnaire	*	-	- Participants collected saliva themselves	- 8 months	- No information available	2	Low
6 Lewis & Hill (2023)	- Unrepresentative sample	* PIL subscale of the Ryff's psychological well-being questionnaire	- PIL was not repeatedly measured in one out of two sample	**	* Independent blind assessment	* 12 years	- No information available	5	Medium
7 Sutin et al. (2023)	* Representative sample	* PIL subscale of the Ryff's psychological well-being questionnaire	- AL biomarkers were not measured at baseline	**	* Independent blind assessment	* 2-4 years	* Description of lost participants was present	7	High
8 Woo et al. (2020)	- Unrepresentative sample	* PIL subscale of the Ryff's psychological well-being questionnaire	- AL biomarkers were not measured at baseline	**	* Independent blind assessment	- Unclear	* Description of lost participants was present	5	Medium
9 Zilioli et al. (2015)	- Unrepresentative sample	* PIL subscale of the Ryff's psychological well-being questionnaire	- AL biomarkers were not measured at baseline	**	* Independent blind assessment	* 10 years	* Description of lost participants was present	6	Medium

Note. *: score fulfilled, −: score not fulfilled/too little information, 1: representativeness of the sample (a * is given when the cohort was truly or somewhat representative of the average population); 2: ascertainment of PIL (a * was given when PIL was measured using a validated questionnaire); 3: demonstration that outcome of interest was not present at start of study (a * was given in case of 'yes'); 4: comparability of cohorts on the basis of the design or analysis (a * was given when the study controlled for

age and sex and an additional * was given when the study controlled for any additional factor); 5: assessment of AL (a * was given when AL was given when biomarkers were measured via independent blind assessment or record linkage); 6: was follow-up long enough for outcomes to occur (a * was given when the follow-up period was 2 years or longer); 7: adequacy of follow-up of cohorts (a* was given in case of a complete follow-up - meaning that all subjects were accounted for or when less than 5% of participants were lost at follow-up or when a description of lost participants was provided).

S3 Table

Vote Counting of Significant Outcomes in All Included Longitudinal Studies and Prospective Cohort Studies

System	Biomarker	Boy. 2015	Fried. 2012	Gian. 2023	Gui. 2022	Hsa. 2014	Lew. 2023	Sut. 2023	Woo. 2020	Zil. 2015	Total
Cardio-vascular	SBP	→r=-.01					ND		ND	r=-.041	0/2
	DBP	→r=-.03					ND		ND		0/1
	HR								ND		0/0
Metabolic system	BMI		→r=-.06	→r=-.18*			ND			→r=-.116**	2/3
	W/H		→r=-.11**						ND		1/1
	Trig	→r=-.12*					ND		ND		1/1
	HDL	→r=.10*					ND		ND		1/1
	LDL								ND		0/0
	Chol						ND				0/0
	IR								ND	→r=-.058	0/1
	Gluc	→r=.01					ND		ND		0/2
	HbA1c						ND		ND		0/0

	WC	→r=-.10*								1/1
Inflammatory system	sE-S							ND	→r=-.07*	1/1
	sICAM-1							ND		1/1
	Fib					ND		ND		0/0
	CRP		→β=.10*	→β=.006	→HR=.96	ND	→β=-.07***	ND		2/4
	IL-6		→β=.05				→β=-.08***	ND		1/2
	IL-1ra						→β=-.08***			1/1
	IL-1β									0/0
	IL-10						→β=-.07***			1/1
	TGFβ-1						→β=.02			0/1
	sTNFR1						→β=-.10***			1/1
Neuro-endocrine system	Cor				MIL-p surv: →β=.009 MIL-s surv: →β=-.007 MIL-p spouse: →β=-.008 MIL-s spouse: →β=.003			ND	→r=-.018	0/5
	DHEA-S							ND		0/0

	E			ND	→r=-.027	0/1
	NE			ND		0/1
	RMSSD			ND	→r=-.076*	1/1
	SDRR			ND		1/1
Other	Cys-c		ND			0/0
Total indexes	AL		HRS: →β=.001 ELSA: →β=-.004	→β=-.002	→β=-.085**	1/4
	MSC	→β=-.11*				1/1

Note. Arrows are used to refer to the direction of the relationship. The provided statistics have been adjusted for covariates whenever they were incorporated into the model. ND means that the AL biomarker was included in the study, but no data was available regarding its relationship to PIL, MIL or SOC.
∗ p<.05; ∗∗ p<.01; *** p<.001.

S4 Table

Vote Counting of Significant Outcomes in All Included Cross-sectional Studies

		Ber. 2023	Cam. 2022	Dav. 2015	Frie. 2007	Gou. 2017	Iro. 2018	Lee. 2022	Lin. 2002	Mar. 2016	Pul. 2018	Ryff. 2006	Svar. 2000	Tan. 2011	The. 2015	Total
Cardiovascular	SBP				ND				ND	→β=.03		→r=-.09	←r=.10*	→r=.07		1/4
	aSBP														MIL: →R2=.070 SOC: →R2=.066	0/2
	pSBP														MIL: →R2=.079 SOC: →R2=.075	0/2
	BP													→r=.32	MIL: →R2=.036 SOC: →R2=.032	0/3
	Chol												ND			0/0
	DBP				ND				ND	→β=-.09			←r=.14*	→r=.45**		2/3

	pDBP							MIL: →R2= .018 SOC: →R2= .032	0/2
	HDL	ND		→β=.30	→r= .22**	←β= 4.546* ←r=.12	→r=.30		2/4
	LDL		ND	→β= -.09		Low SOC: ←F=3.5 Med SOC: ←F=3.5 High SOC: ←F=3.7			0/2
	Tot/HDL	ND			→r=-.15		→r= -.39*		1/2
	Trig		ND			←β= -.536 ←r= -.12*	→r= -.19		1/3
Metabolic system	W/H	ND			→r=-.17 *		→r= -.17		1/2
	We					←r=.10*			1/1

	BMI	→β= .101				ND	→β= -1.09*	→r=-.15	←β= .934***	→r=.16	2/5
	BF									→r=.03	0/1
	HbA1c		ND							→r= -.04	0/1
	Gluc						→β= -.05		Low SOC: ←F=6.6 Med SOC: ←F=6.7 High SOC: ←F=6.5		0/2
	HbA1c							→r=-.13		→r= -.04	1/4
	WC	M: →β= -.075** C: →β= -.104									
	IR									→r= -.19	0/1
Inflammatory system	CRP			ND	→β= -.011	→β= -.07	→β= -.06			→r= -.23	0/4
	IL-6		→β= -.05	→β= −0.181		→β= -.58*	→β=-.15				2/4

m				*					
	MMP-9					→β=-1.84*			1/1
	sIL-6R		→β=-.24*						1/1
	IL-1β			→β=-.61**					1/1
Neuroendocrine system	Cor		ND		→r=-.44*	→r=-.03	→r=.29*		2/3
	Mor Cor				→r=-.35				0/1
	DHEA-S						→r=-.05		0/1
	Cat				ND				0/0
	E		ND		ND		→r=.02		0/1
	NE	→r=-.21*	ND		ND		→r=-.02		1/2
		→β=-.24*							
Total indexes	AL							→r=-.29	0/1

Note. Arrows are used to refer to the direction of the relationship. The provided statistics have been adjusted for covariates whenever they were incorporated into the model. ND means that the AL biomarker was included in the study, but no data was available regarding its relationship to PIL, MIL or SOC.
∗ p<.05; ∗∗ p<.01; *** p<.001.