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Nonuniversality of inflammaging across human populations

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Maximilien Franck[1] ✉, Kamaryn T. Tanner[2], Robert L. Tennyson[3,4], Camille Daunizeau[5], Luigi Ferrucci[6], Stefania Bandinelli[7], Benjamin C. Trumble[8], Hillard S. Kaplan[9], Jacob E. Aronoff[8], Jonathan Stieglitz[10], Thomas S. Kraft[11], Amanda J. Lea[3], Vivek V. Venkataraman[12], Ian J. Wallace[13], Yvonne A. L. Lim[14], Kee Seong Ng[15], Joe Poh Sheng Yeong[16,17,18,19], Roger Ho[20], Xinru Lim[16], Ameneh Mehrjerd[21], Eleftheria G. Charalambous[21], Allison E. Aiello[2,22], Graham Pawelec[23,24], Claudio Franceschi[25], Johannes Hertel[21,26], Tamàs Fülöp[1], Maël Lemoine[27], Michael Gurven[28] & Alan A. Cohen[1,2,29] ✉

Inflammaging, an age-associated increase in chronic inflammation, is considered a hallmark of aging. However, there is no consensus approach to measuring inflammaging based on circulating cytokines. Here we assessed whether an inflammaging axis detected in the Italian InCHIANTI dataset comprising 19 cytokines could be generalized to a different industrialized population (Singapore Longitudinal Aging Study) or to two indigenous, nonindustrialized populations: the Tsimane from the Bolivian Amazon and the Orang Asli from Peninsular Malaysia. We assessed cytokine axis structure similarity and whether the inflammaging axis replicating the InCHIANTI result increased with age or was associated with health outcomes. The Singapore Longitudinal Aging Study was similar to InCHIANTI except for IL-6 and IL-1RA. The Tsimane and Orang Asli showed markedly different axis structures with little to no association with age and no association with age-related diseases. Inflammaging, as measured in this manner in these cohorts, thus appears to be largely a byproduct of industrialized lifestyles, with major variation across environments and populations.

Inflammaging, defined as an age-associated increase in systemic markers of chronic, low-grade inflammation, is considered a hallmark of aging in Mammalia[1–3]. Inflammaging is elevated with many chronic, age-related diseases (CARDs), acting as a key pathogenic mechanism[4]. In some nonindustrialized populations (NIPs) with constitutively high inflammation from infections[5,6], there is minimal incidence or pathology of the key CARDs of industrialized societies: coronary artery calcification, diabetes, Alzheimer's disease and various cancers[7–9]. This stark ecological distinction raises important questions about the nature of inflammaging[10]: if it is indeed a universal aging mechanism, it should be measurable and impact pathology in NIPs.

A challenge is that there is no definitive measurement framework for inflammaging. Conceptual models (for example, macrophage stress response[3], NF-κB hyperactivation[11], cytokine/chemokine profiles[12,13] and immunosenescence[14]) are complex and not directly translatable across scales and species. However, if cellular inflammaging has a predictable impact on organismal aging, consistent cytokine signatures and pathological consequences are expected. Previously, principal components analysis (PCA) on 19 inflammatory signaling cytokines in the Invecchiare in Chianti, aging in the Chianti area (InCHIANTI) dataset from Italy identified a robust characterization of inflammaging[13,15], a key first axis largely driven by simultaneous activation of soluble

A full list of affiliations appears at the end of the paper. ✉e-mail: maximilien.franck5@gmail.com; aac2277@cumc.columbia.edu

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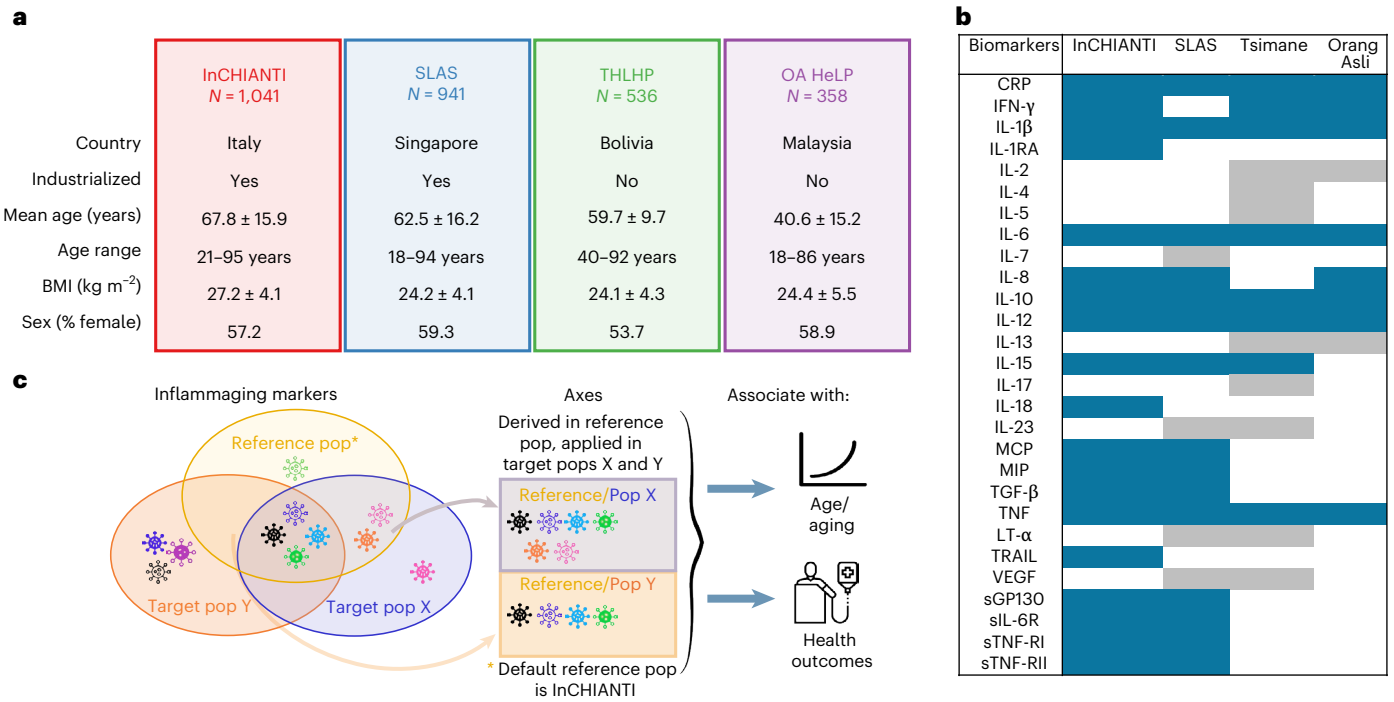

Fig. 1 | Study design. a, The demographic data on the included cohorts. The sample size indicates complete cases used in this study. **b**, The cytokines used by dataset. Shading indicates the presence of each biomarker, with blue highlighting those common with the InCHIANTI cohort and gray for cytokines absent in InCHIANTI. **c**, Identification of common sets of cytokines and workflow. One population (pop) is chosen as a reference population, and cytokines that overlap with target populations are identified. Interpretation of axes and stability across cytokine sets is verified and these are then related to age and health outcomes. Primary analyses use InCHIANTI as the reference population and sensitivity analyses replicate this from the perspective of each other population.

tumor-necrosis factor receptor I (sTNF-RI), sTNF-RII, interleukin (IL)-6, C-reactive protein (CRP), IL-18 and tumor-necrosis factor (TNF). Scores on this axis increased markedly with age and predicted the risk of many CARDs. Here, we replicate that analysis in an industrialized Singaporean population (Singapore Longitudinal Aging Study (SLAS)), and in two Indigenous NIPs with high levels of infection-related inflammation and low levels of CARDs: the Tsimane from the Bolivian Amazon (Tsimane Health and Life History Project (THLHP)) and the Orang Asli from Peninsular Malaysia (Orang Asli Health and Lifeways Project (OA HeLP)). Most studied immune parameters are high in both populations (for example, immunoglobulins and CRP), primarily due to their highly pathogenic environments[5,6]. The Tsimane demonstrate a high resting metabolic rate and low cholesterol levels, probably due to a combination of pathogens, a lean fibrous diet and high physical activity[16]. Meanwhile, the Orang Asli display greater lifestyle heterogeneity, with some maintaining traditional subsistence lifestyles and others undergoing advanced stages of epidemiological transition[17].

Results

We analyzed existing cytokine data from InCHIANTI, SLAS, THLHP and OA HeLP (Fig. 1). As cytokines were measured using different platforms, absolute levels are not directly comparable, and available cytokines differ (Fig. 1b). To circumvent this problem, each population was used in turn as the 'reference' population, and results were replicated in the other 'target' populations using the overlapping subsets of cytokines (Fig. 1c).

Patterns of cytokine variation differ across populations

Given its prior validation[13], we used InCHIANTI as the primary reference population. To do this, we extracted the first axis from the full set of cytokines in each dataset and assessed whether it was similar to the axis identified in InCHIANTI (Fig. 2). Owing to the clear theoretical justification for an inflammaging axis, here we use factor analysis (FA) with varimax rotation; PCA results are similar (Extended Data Fig. 1). The first column of Fig. 2 shows consistency of the inflammaging factor in InCHIANTI across analyses decreasing inclusion of the 19 cytokines (Fig. 2a) to the 16 that overlap with SLAS (Fig. 2b) to the 8 each that overlap with THLHP (Fig. 2e) and OA HeLP (Fig. 2h). For OA HeLP, factors 1 and 2 switch order, but interpretation is conserved. Strong correlations among the scores generated by these different versions of the inflammaging axis confirm this (Extended Data Fig. 2b). Additional biplots show how closely the axis structure replicates across sexes (Extended Data Fig. 3).

Next, we assessed whether the axis structure for these overlapping subsets was reproduced in SLAS, THLHP and OA HeLP. In SLAS (Fig. 2c), the axis structure was similar but not identical, with loadings correlated at $r = 0.70$. The first axis, representing inflammaging, was defined strongly by sTNF-RI and sTNF-RII and more moderately by CRP, TNF, soluble (s)GP130 and sIL-6R. IL-6 was not associated with either of the two factors and IL-1RA and IL-15 shifted to the second factor. In THLHP and OA HeLP, in contrast, axis structure differed completely (Fig. 2f,i) from InCHIANTI (Fig. 2e,h), with the first factor loadings correlated at $r = -0.42$ and -0.15 respectively. Specifically, the key inflammaging markers in InCHIANTI—CRP, IL-6 ad TNF—do not align on one axis in OA HeLP. Axis structure in all datasets changes only minimally when adding additional cytokines not measured in InCHIANTI (Fig. 2d,g,j).

To ensure that the axis structures were not artifacts of a few aberrant samples, we replicated the analysis in subsets of each population stratified by sex, age and health status (Supplementary Table 1). The loadings of the inflammaging factor derived from these various subsets are almost perfectly correlated ($r > 0.92$, Fig. 2k and Extended Data Fig. 3), indicating remarkable stability of the axis structure replicated even in mutually exclusive subsamples. This eliminates concerns about artifacts from study sample age ranges (Fig. 1a). Broadly, Fig. 2 shows that axis structure is highly replicable within populations across marker sets and demographic subgroups. Even in the absence of two key cytokines—sTNF-RI and sTNF-RII—basic axis structure is replicated.

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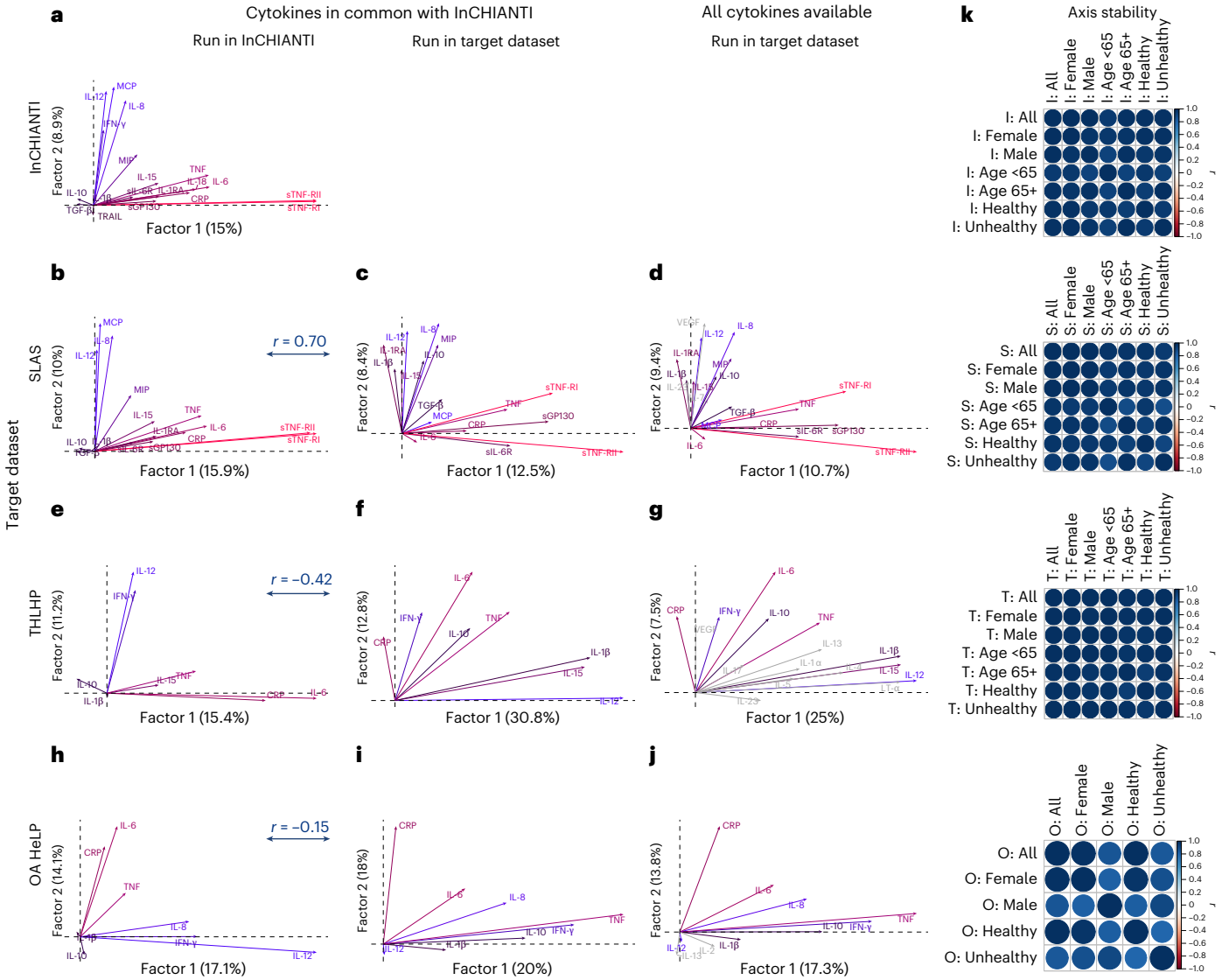

Fig. 2 | Key factors replicate within, but not across, datasets. a–**j**, Biplots showing the associations of cytokines with the first two factors run in different datasets and with different sets of cytokines: the first column (**a**, **b**, **e** and **h**) shows analyses run in InCHIANTI, but with subsets of cytokines that overlap with those available, respectively, in the full InCHIANTI set (**a**), SLAS (**b**), THLHP (**e**) and OA HeLP (**h**); the second column (**c** for SLAS, **f** for THLHP and **i** for OA HeLP) shows the axis structure of the same cytokines as in column 1 (**b**, **e** and **h**, respectively), except run in the target datasets, not InCHIANTI; the third column (**d** for SLAS, **g** for THLHP and **j** for OA HeLP) replicates the analysis in the second column but adding in the cytokines not measured in InCHIANTI (light gray). The colors of each arrow are reproduced from **a** across all graphs to facilitate comparison, with red indicating strong association with the first factor in **a**, purple with the second factor and black with the origin (no association). A color pattern similar to **a** thus indicates a similar axis structure. Correlation coefficients between columns 1 and 2 show the Spearman correlations of the loadings between the indicated graphs. **k**, Pairwise correlations between the loadings of the inflammaging factor when derived in the full population, just male subjects, just female subjects, just age <65years, just age 65+ years and with or without chronic disease diagnoses. I, InCHIANTI; S, SLAS; T, THLHP; O, OA HeLP. All correlations in **k** are significant at $P \leq 0.01$ ($P < 0.0001$ for InCHIANTI, SLAS and THLHP) based on a two-sided t-test without multiple comparison adjustment.

We then replicated the analysis from Fig. 2, shifting the reference population from InCHIANTI to each of the other populations. These analyses confirm that the first SLAS factor is similar but not identical to the InCHIANTI factor, with composition concordant with classic notions of inflammaging (Extended Data Fig. 4). In contrast, the first THLHP and OA HeLP factors do not replicate in the other populations—including each other—and do not have cytokine compositions consistent with inflammaging (Extended Data Figs. 5 and 6). The result was never sensitive to which cytokines were included or excluded. Population differences in axis structure do not reflect absolute cytokine levels, which are generally high in THLHP and lower in OA HeLP (Supplementary Fig. 1). For example, sTNF-RI, sTNF-RII and sGP130 are much higher in InCHIANTI than SLAS, but nonetheless strongly load on the first axis in both. In contrast to InCHIANTI and SLAS, individual cytokines correlate only weakly with age in THLHP and OA HeLP (Supplementary Figs 1 and 2).

Next, we analyzed pairwise correlations in each dataset among the seven key cytokines associated with the first axis in InCHIANTI (Fig. 3). In InCHIANTI, unsurprisingly, all seven are positively correlated. In SLAS, IL-6 and IL-1RA are uncorrelated with the other cytokines. In the Tsimane, CRP shows only a weak association with IL-6. Correlations are present among these three cytokines in the Orang Asli.

Associations of inflammaging with age and health outcomes vary across populations

We then assessed associations of the inflammaging factor scores with age and health outcomes in each dataset (Fig. 4). We used the

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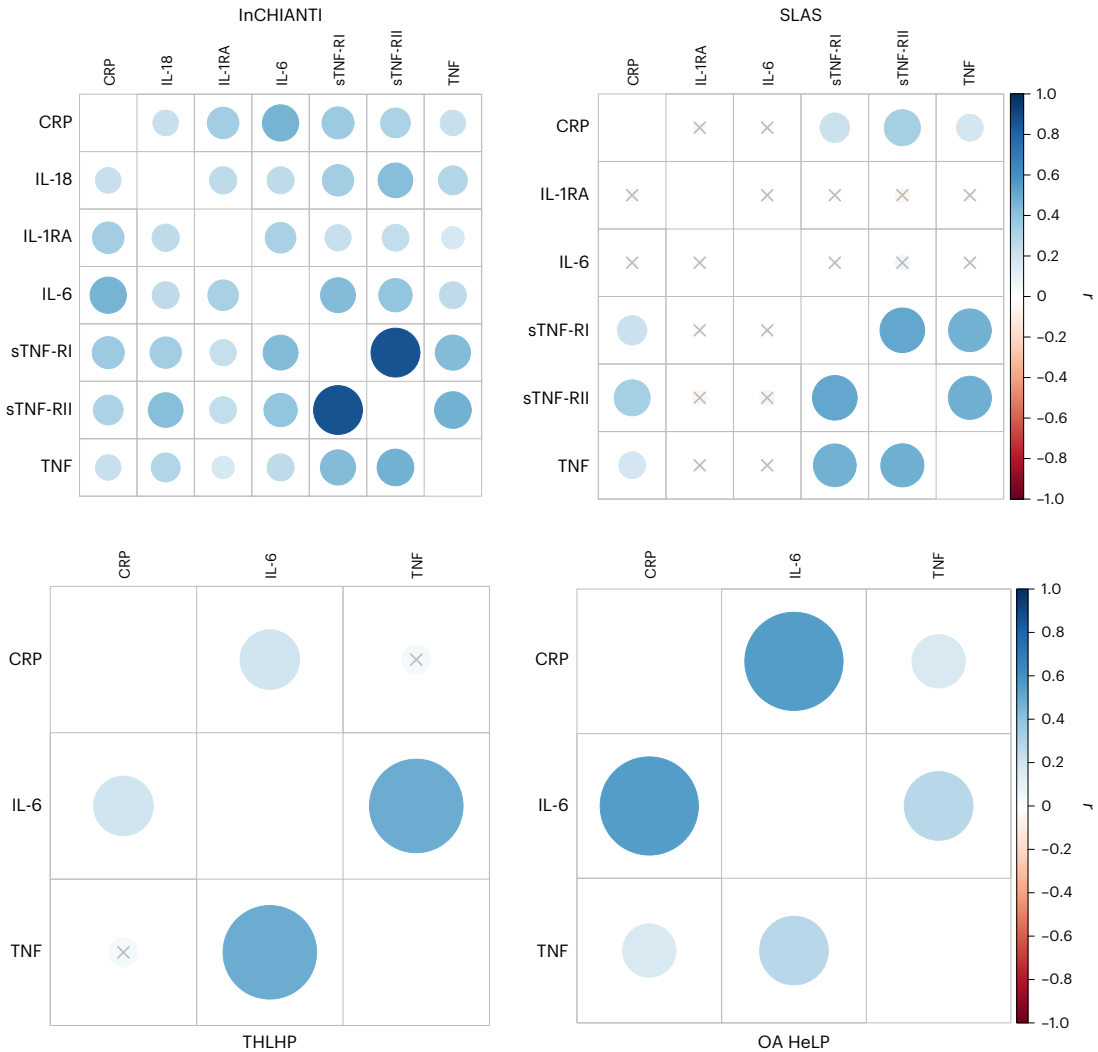

Fig. 3 | Spearman correlations among key inflammatory cytokines in each dataset. The seven cytokines most strongly associated with the first factor in InCHIANTI are plotted in a pairwise correlation matrix; for subsequent datasets, the subset of those seven that were measured in the dataset are plotted. An X indicates that the correlation is not significant at $\alpha = 0.05$.

inflammaging factor loadings derived in InCHIANTI (that is, those shown in Fig. 2a,b,e,h) applied to the respective target datasets (InCHIANTI, SLAS, THLHP and OA HeLP) to approximate the InCHIANTI axis as closely as possible in each of the other datasets. Associations with age are shown in Fig. 4a, ranging from strong in InCHIANTI to moderate in SLAS, weak in OA HeLP and absent in THLHP.

Associations of inflammaging with CARDs are similar in InCHIANTI and SLAS (Fig. 4b). For both, the strongest association is with chronic kidney disease (odds ratios (ORs) of ≈5). Which other diseases show significant associations differs between datasets, though confidence intervals generally overlap.

Associations with CARDs are challenging to assess in THLHP and OA HeLP owing to the low prevalence of these conditions[8,18]. We present data only for the outcomes where sufficient sample size allowed models to converge. In THLHP (Fig. 4c), neither arthritis nor high blood pressure is associated with inflammaging, though they are also not associated in InCHIANTI. However, for chronic kidney disease, THLHP (OR of 0.84) strikingly fails to replicate the strong association in InCHIANTI (OR of 2.83). Neither high blood pressure nor diabetes was associated with inflammaging in OA HeLP (Fig. 4d).

We next replicated the analyses in Fig. 4, but with each other dataset as the reference population. As noted above, the first factors for THLHP and OA HeLP cannot be considered inflammaging proxies. The first SLAS factor increases sharply with age in InCHIANTI and SLAS, but not at all in THLHP or OA HeLP (Extended Data Fig. 7a). It also predicts chronic disease in both SLAS and InCHIANTI, but not in THLHP or OA HeLP (Extended Data Fig. 7b–d). The first THLHP factor increases slightly with age in InCHIANTI and OA HeLP but decreases sharply with age in SLAS and shows no significant change in THLHP itself (Extended Data Fig. 8A). It is associated with kidney disease in InCHIANTI, but more weakly than other axes, and is unassociated with any other chronic conditions in any population (Extended Data Fig. 8b–d). The first OA HeLP factor increased with age in InCHIANTI, SLAS and slightly in OA HeLP (Extended Data Fig. 9a). It predicted a few chronic conditions, but less strongly than the InCHIANTI and SLAS factors (Extended Data Fig. 9b–d).

Last, we examined the consistency of relationships with upstream factors that might impact inflammaging. Data on smoking and body mass index (BMI) were available in all populations. Additionally, in THLHP and OA HeLP, data on eosinophilia (indicating helminth infections) and leukocyte count (a generalized indicator of infection) quantified infection status. Both BMI and smoking were positively associated with inflammaging scores in InCHIANTI and SLAS (Extended Data Table 1). However, in OA HeLP, BMI but not smoking was associated with the inflammaging axis, while neither was in THLHP. Leukocytosis,

but not eosinophilia, was generally associated with inflammaging in THLHP and OA HeLP.

Discussion

Our results document that an inflammaging axis structure that is robust and highly replicable within two industrialized populations differs only moderately between them, but markedly from two NIPs. The NIPs show little to no change in inflammaging with age nor association with measured CARDs. As techniques such as PCA and FA rely on the variance within the datasets, this can be interpreted as meaning that individuals in THLHP and OA HeLP show little variation in levels of inflammaging relative to other sources of variation in cytokines.

Our analyses showed that these differences are relatively independent of which cytokines are measured. Differences might be attributable to different sample handling, storage or assay platforms. However, sample handling and storage were similar between datasets (for example, there was no delay in freezing in NIPs; Supplementary Table 2). The lack of harmonized outcome data is a limitation, but is inevitable given that these diseases are rare in these populations and/or may not be similarly diagnosable[7–9,18,19].

Nonetheless, our findings are supported by the rarity of CARDs in the Tsimane, despite their elevated and variable cytokine levels and inflammaging factor scores[5] (Extended Data Fig. 2A, Fig. 4a, Supplementary Fig. 1). Such high variation without a clear dimension in FA means that other dimensions are even more variable. Mortality selection in THLHP and OA HeLP could contribute to these patterns but is unlikely to be a sufficient explanation, given the rarity of CARDs as a cause of death.

How can we reconcile our findings with the wealth of evidence that inflammaging generalizes across species[11,20,21], including great apes?[22] No studies in other species have used a definition similar to ours, making comparisons challenging. Inflammaging at a cellular or tissue level might be more similar than circulating cytokine profiles across populations. Cytokines have multiple sources, targets and half-lives. Their pleiotropic, versatile and redundant nature allows fine-tuned signaling to achieve context-specific outcomes[23]. Hence, circulating cytokines are not mere byproducts released from damaged cells and tissues; rather, they are signals that integrate information about the state of the organism across these cells and tissues, coordinating a coherent, whole-organism response[24,25]. Diverse stressors and exposures may cause wide variability in blood signaling molecules, potentially obscuring any universal cytokine signature and resulting in context-dependent pathophysiological outcomes. Accordingly, we see three related possibilities: (1) cellular inflammaging exists in NIPs but manifests very differently at the organismal level or has minimal consequences due to complex physiological buffering; (2) inflammaging may not be exclusively pathological[10]: there may be a fine line between an adaptive response and an excessive pathological response, or inflammaging may be making the best of a 'bad' physiological situation[26–28]; and (3) the inflammaging that generalizes is a broad suite of loosely related processes[11,20], less specific than our definition based on circulating signatures in InCHIANTI. Compositions of two inflammatory clocks recently developed in US and Russian populations were quite different and overlapped only weakly with each other or with the cytokines used here[12,14]. Overall, this supports the lack of a specific, universal signature in humans.

Genetic differences among populations may contribute to absence of InCHIANTI-like inflammaging in nonindustrial societies[29,30]. Comparative genomic analysis demonstrates that the Tsimane possess distinct allelic frequencies in regions related to immune and metabolic functions[31,32]. However, population-specific immune genetics[33] are unlikely to fully explain our results, given (1) failure to replicate associations between cytokine gene polymorphisms and CARD risk across populations[34], (2) the comparatively small role of genetics in immune variation[35] and (3) the industrialized/nonindustrialized split regardless of ancestry.

Given this, we believe that differences in the exposome—lifestyle, environmental and infectious—are a major factor. With only four populations, we cannot directly test for such drivers, particularly since THLHP and OA HeLP differ radically from InCHIANTI and SLAS in many ways: diet, physical activity levels, exposure to pollutants, fertility and so on, with greater inter- than intrapopulation variation. However, we found that smoking did not predict inflammaging at the individual level in either THLHP or OA HeLP, and BMI did not in THLHP, suggesting that population-level rather than individual factors might be driving the differences.

One of the most intriguing hypotheses for such exposome differences is the infectious environment. Many THLHP and OA HeLP individuals have ongoing infections at any given time, leading to major differences in cytokine profiles. Indeed, much cytokine variation in these populations is probably due to the type and severity of current infections, not aging. Roughly 66% of Tsimane have at least one intestinal parasitic infection: 30–40% of adults present with a gastrointestinal infection, 20–30% have a respiratory infection, 25% leukocytosis and 86% eosinophilia[36,37]. In the Orang Asli, 70% have a prevalent infection: 27% respiratory, 22% fungal, 30% leukocytosis and 41% eosinophilia. Additionally, helminths, which are common among the Tsimane and Orang Asli, may have protective effects[5,38,39]. Helminth infection induces Th2 responses that stimulate innate immunity and M2 macrophages while dampening other inflammatory processes[40,41]. However, inflammaging may not always be absent in high-infection environments[42]. We found no association between eosinophilia and inflammaging in THLHP or OA HeLP at the individual level, but this does not exclude the possibility that common helminth infections restructure the immune system in other ways. Regardless, our results show that cytokines are not destiny with regard to inflammaging and chronic disease.

While InCHIANTI and SLAS results broadly align, key differences emerge at a finer scale. Notably, IL-6—often considered a key marker of inflammaging—showed no correlation with age or with cytokines in SLAS. Additionally, IL-15 and IL-1RA shift from the first axis to the second, and sTNF-RI and sTNF-RII are less tightly coupled. These small differences in axis structure were replicated in intrapopulation analyses and persist even when stratifying by sex, age and health status (Fig. 2k and Extended Data Fig. 3). We lack a definitive explanation for these differences. Even within industrialized populations, manifestation of inflammaging is highly heterogeneous[14,28,43]. The replication by health status in Fig. 2k implies that inflammaging is not simply a result of chronic conditions. This is partially consistent with findings from Terekhova et al.[44] showing age-specific differences in immune cell repertoire among a healthy US cohort, despite minimal differences in inflammatory signatures.

Our findings thus challenge the notion that inflammaging, as commonly conceived and measured epidemiologically, is an aging mechanism per se. Rather, it may reflect immune dysregulation resulting from an evolutionary mismatch of physiology and environment[10,18]. This aligns with the notion that the hallmarks of aging are not universals, but rather common manifestations whose importance varies by context[45]. However, such conclusions hinge on how inflammaging is defined; here, we are limited to using the circulating cytokine profiles observed in InCHIANTI.

Our results are part of a broader trend questioning the generalizability of health-related findings from high-income populations[7,10]. Previous findings in the Tsimane include the absence of most heart disease despite low high-density lipoprotein and high CRP levels[8,46] and lower risk of cognitive impairment for carriers of the APOE4 allele under conditions of high helminth infection[36]. These findings suggest an organismal capacity for broad physiological remodeling, achieving diverse alternative stable states depending on conditions. Not only the levels but also the interactions among molecules/components change. This parallels findings at the biochemical level where protein–protein interaction networks differ markedly across cell types[47] and reinforces

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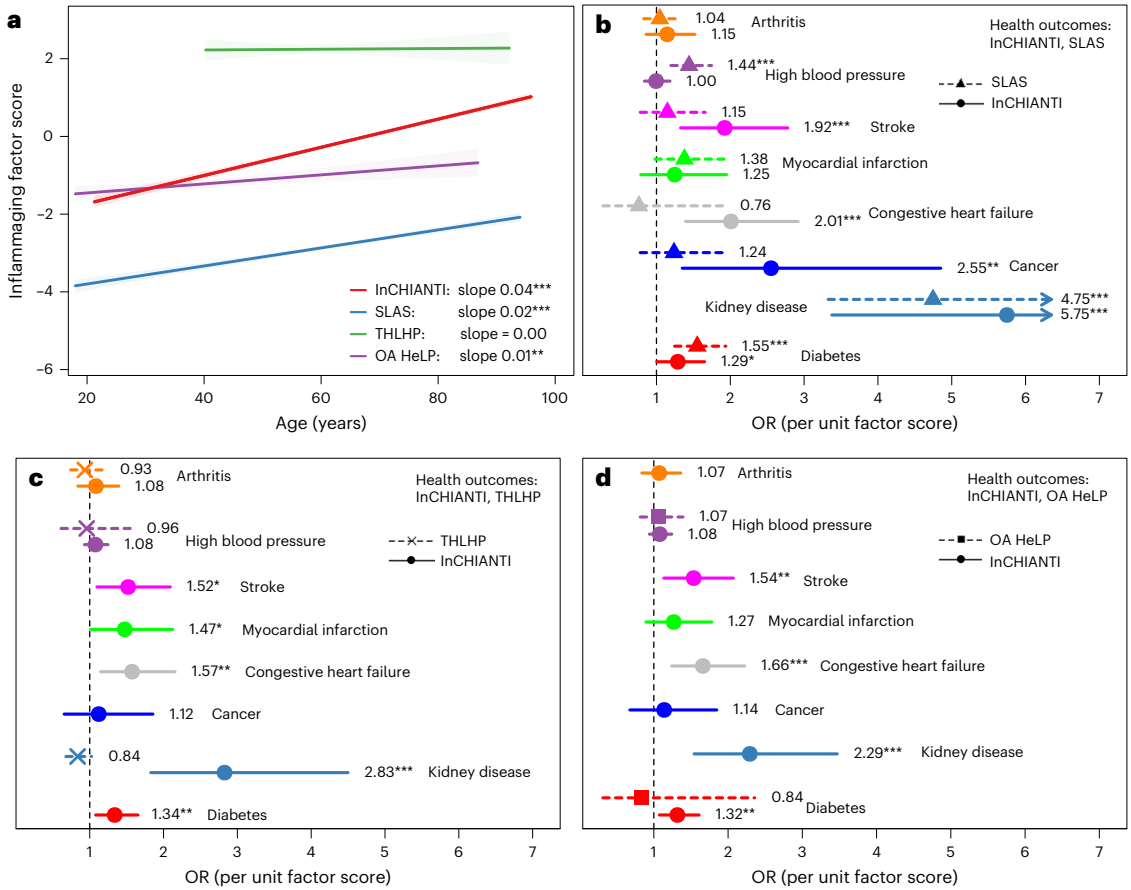

Fig. 4 | Associations of the inflammaging factor with age and health outcomes. a, Associations between the inflammaging factors derived in Fig. 2a,b,e,h with age, when applied in the respective datasets. The shaded region is a 95% confidence interval for the best-fit lines shown. *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$, based on a two-sided Wald test. **b**, A comparison of the predictions of health outcomes in InCHIANTI and SLAS using the inflammaging axis derived in Fig. 2b. **c**, A comparison of the predictions of health outcomes in InCHIANTI and THLHP using the inflammaging axis derived in Fig. 2e. Not all outcomes are available in THLHP. **d**, A comparison of the predictions of health outcomes in InCHIANTI and OA HeLP using the inflammaging axis derived in Fig. 2h. Not all outcomes are available in OA HeLP. In **b**–**d**, the points indicate the estimated OR and the lines show the 95% confidence interval. The vertical line indicates no effect. *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ based on a two-sided Wald test. The ORs are scaled per unit factor score. As factor score ranges are 6+ within populations (Extended Data Fig. 2a), an OR of 1.5 translates into at least $1.5^6 = 11.4$ across the range of values in the populations. Note that different ORs for InCHIANTI in **b**, **c** and **d** are due to different versions of the inflammaging axis using overlapping biomarker sets with the other datasets. Number of biological replicates: InCHIANTI (1,041), SLAS (941), THLHP (536) and OA HeLP (358). Supplementary Table 1 details the availability of health outcomes by dataset.

an understanding of biological networks as constantly adapting to changing conditions. In this context, cytokine networks dynamically shift to coordinate functions across the organism in a changing environment. Processes such as inflammaging may be conditional processes that help an organism navigate specific circumstances. Much work remains to illuminate this cytokine code.

Our findings have practical and theoretical implications. To the extent that inflammaging and related processes are population specific, more work is needed to predict the conditions under which patterns of inflammaging converge or diverge. Studying wide intrapopulation lifestyle gradients[18] and/or which environmental or population-level factors influence inflammaging may provide avenues to decrease either its prevalence or its consequences. Future studies should replicate our findings using a standardized cytokine panel across cohorts, run jointly on mixed plates, including markers such as CXCL9 needed for other clocks[12,14]. Standardized measures of context-related risk factors are also needed[48], the striking absence of sex differences should be probed and functional outcomes added for more standardized measures. Last, the first factors in THLHP and OA HeLP differ markedly from each other, and their biological relevance should be studied.

On the basis of our results, inflammaging, as commonly conceptualized epidemiologically, is not a quantitatively or qualitatively universal aspect of human aging. Large population- and context-dependent historical and geographical differences should be expected and specifically addressed. While it appears to be a common and important process under industrialized conditions, this may result from a mismatch between immune genetics and pathogen environment. Even where present, the impacts of inflammaging on CARD risk appear heterogeneous (Fig. 4b). More generally, these findings challenge the assumption that human physiological processes are universal and can be extrapolated from one population to others. Understanding the context dependence and contingency of the biology underlying aging and CARDs will have profound implications for both the biology and epidemiology of aging.

Methods

Human subjects statement

Informed consent was obtained for all study participants in all cohorts—written consent for literate individuals, and verbal consent with thumbprint otherwise. THLHP data collection was approved by the University of New Mexico (no. 07-157) and the University of California, Santa

Barbara (no. 3-21-0652) Human Subjects Review Committees. For the Tsimane participants, written informed consent was provided after procedures and risks were explained in their native language, with approvals from each village and the Tsimane Government (Gran Consejo). OA HeLP data collection was approved by the Medical Review and Ethics Committee of the Malaysian Ministry of Health (protocol ID NMRR-20-2214-55565), the Malaysian Department of Orang Asli Development (permit ID JAKOA.PP.30.052 JLD 21 (98)) and the Institutional Review Board of Vanderbilt University (protocol ID 212175). Community-level approval was obtained before recruitment, and written informed consent was obtained from all participants. SLAS data collection was approved by the National University of Singapore Institutional Review Board (ref. L04-140C). Participants in SLAS provided written informed consent. InCHIANTI data collection was approved by the Ethical Committee at INRCA, Ancona (protocol 14/CE, 28 February 2000) and FU1 (protocol 45/01, 16 January 2001); participants provided written informed consent. Secondary analysis was approved by the University of Sherbrooke Ethics Board (ref. 2019-2657) and Columbia University Medical Center's Institutional Review Board (no. AAAU5622).

Data

In this secondary data analysis, we use data from four cohort datasets: InCHIANTI, SLAS, THLHP and OA HeLP. The InCHIANTI cohort was designed to study factors related to mobility loss as individuals age and is comprised primarily of individuals aged 65 years or more living in the Tuscany region of Italy[49]. Initial data on 1,453 participants were collected in 1998–2000. This study used data on a subset of 1,041 participants who had complete data on the biomarkers of interest (see 'Cytokines' section). SLAS is a population-based study of adults over 55 years of age residing in Singapore[50]. Initial assessment of 2,804 individuals in 2003–2004 collected biological, clinical, behavioral and social data. We use a subset of 941 people. THLHP aims to study aging across the human life course of an Amerindian tribe of forager–horticulturalists living in the Bolivian Amazon[37]. This cohort is comprised of individuals from >90 villages with subsistence lifestyles and low levels of industrialization. Baseline data included demographics, biomarkers, inflammation, physical status, behavioral factors and exposure to infectious agents. Here, data from 536 individuals were utilized. The OA HeLP cohort contains biospecimen and ethnographic data on Indigenous peoples of Peninsular Malaysia, known collectively as the Orang Asli[17]. The sample of participants used in this study live in a range of community types from remote rain forest camps to peri-urban settlements with increased access to modern medical facilities, market goods and sanitation; the changing environment from traditional lifestyles to more modern ones and its impact on noncommunicable diseases is the focus of OA HeLP. On the basis of availability of relevant cytokine data, we used data on a subset of 358 individuals from across this urbanicity gradient[48], about 120 of whom were from peri-urban settlements. Most were younger (326 under age 65 years).

Cytokines

We used a core set of 19 inflammaging biomarkers identified in Morrisette-Thomas[13] and found in InCHIANTI: CRP, interferon (IFN)-γ, IL-1β, IL-1RA, IL-6, IL-8, IL-10, IL-12, IL-15, IL-18, monocyte chemoattractant protein (MCP), macrophage inflammatory protein (MIP), transforming growth factor (TGF)-β, TNF, TNF-related apoptosis-inducing ligand (TRAIL), sGP130, sIL-6R, sTNF-RI and sTNF-RII. Availability of data on these cytokines varies by dataset (Fig. 1b). SLAS contains data on 16 of these cytokines, while THLHP and OA HeLP each hold data on eight. Data for those cytokines that overlap with the 19 from InCHIANTI formed the basis for our analyses. We also present FAs containing biomarkers unique to each cohorts: IL-7, IL-23 and vascular endothelial growth factor (VEGF) for SLAS; IL-4, IL-5, IL-13, IL-17, IL-23, lymphotoxin-alpha (LT-α) and VEGF for THLHP; and IL-2 and IL-13 for OA HeLP. Details of sample storage and cytokine measurement by dataset are provided in Supplementary Table 2. Several cytokine values were below the limit of detection (BLD), particularly in SLAS. To address this, we used multiple imputation methods, generating values within the range between zero and the detection limit (Supplementary Methods). In InCHIANTI, BLD values that were provided as 0 were replaced with the minimum detection value divided by 2. These approaches aimed to prevent potential biases that could arise from treating BLD values as missing data, as they still provide important information about cytokine levels.

Health outcomes

We tested associations of the derived inflammaging axes with various health outcomes including high blood pressure, stroke, congestive heart failure, diabetes, arthritis, cancer, myocardial infarction and kidney disease. The availability of data on health outcomes varies by dataset (Supplementary Table 1). Each outcome is a binary variable (1: condition present, 0: condition absent) reported at baseline.

In the InCHIANTI cohort, high blood pressure, stroke and congestive heart failure were diagnosed via self-report, physical examination, medication or other documentation. Kidney disease was indicated if there was impaired renal function (measured by 24 h creatinine clearance or Cockcroft–Gault) or a self-reported kidney failure. A definitive diagnosis was assigned if two or more criteria for the above comorbidities were met. Cancer was identified if there was a self-report of a malignant neoplasm within the past 5 years. Occurrence of myocardial infarction within a year was determined by self-report, documentation or electrocardiogram. Diabetes mellitus was diagnosed via laboratory results indicating hyperglycemia (fasting blood glucose >126 mg dl^{-1}), self-report, medication or diet. Arthritis was diagnosed by self-report.

For SLAS[51], research nurses diagnosed chronic conditions at individuals' homes via self-report of physician diagnoses, measurements and details of medications. High blood pressure was defined by self-report, antihypertensive medication use or blood pressure systolic >160 or diastolic >90 mmHg. Diabetes was diagnosed using self-report, use of antidiabetic medication or fasting blood glucose >7.0 mmol l^{-1}. Myocardial infarction and congestive heart failure were determined based on self-report of a physician diagnosis or record of procedures or surgeries or use of cardiac medications.

In THLHP, high blood pressure was defined as systolic >140 and/or diastolic >90 mmHg. Systolic and diastolic blood pressure were measured using an Omron 5 Series upper arm blood pressure monitor. Two consecutive measurements were taken, using the second for analysis (except in the rare case where only one was available). Arthritis (joint inflammation) was diagnosed by a licensed Bolivian physician based on the presence of redness, increased heat and swelling in the affected joint across nine anatomical regions (ankle, elbow, wrist, hip, hand, cervical spine, knee, shoulder and dorsolumbar spine). Additionally, clinicians assessed pain upon pressure application and movement, as well as the joint's functional capacity and movement restriction. Kidney disease was diagnosed as an estimated glomerular filtration rate of less than 60 ml min^{-1}, based on Cockcroft–Gault. Kidney disease is highly prevalent among the Tsimane (53% in the sample used here). This might be partially due to the use of estimated glomerular filtration rate estimating equations that have not been fully validated in the Tsimane or similar populations; the reasons are not well understood. Diabetes mellitus was diagnosed via laboratory results indicating hyperglycemia (fasting blood glucose >126 mg dl^{-1}), but due to the extremely low prevalence of diabetes (only two diagnosed cases in our subset), this condition was not included in the analyses.

For OA HeLP, systolic and diastolic blood pressure were measured using an Omron 5 Series upper arm blood pressure monitor. Two consecutive measurements were taken on each individual, and the second measurement was used for analysis (except in the rare case where only one measurement was available). Hypertension was assigned for any cases where systolic blood pressure was >140 or diastolic blood pressure was >90 mmHg. Diabetes was characterized using measurements

of nonfasting blood glucose and glycated hemoglobin (HbA1C). All individuals were measured for nonfasting blood glucose, and HbA1C tests were performed for any individuals with glucose values >100 mg dl^{-1}. We categorized individuals as diabetic if HbA1C was ≥6.5%, and not diabetic if HbA1C was <6.5% or blood glucose was less than 100 (in which case no HbA1C test was performed).

Statistical analyses

Our analytic plan aimed to assess convergence across as many possible analytical variations and assumptions as possible. The results presented here—a subset of many analyses with different cytokine sets, calibrations, assumptions and additional datasets—are representative and digestible for the reader. For example, the US Health and Retirement Study produces results concordant with InCHIANTI and SLAS, but a limited set of biomarkers made inclusion challenging. Additional details are available upon request.

To assess the monotonic relationships between cytokines within each cohort, we computed Spearman correlation coefficients. We then used exploratory FA with varimax rotation to uncover underlying factors comprised of intercorrelated variables that explain patterns in the data. We performed FA in InCHIANTI using all 19 cytokines, 16 overlapping with SLAS and each 8 overlapping with THLHP and OA HeLP. We also computed factors for SLAS, THLHP and OA HeLP using (1) the cytokines that overlap with InCHIANTI and (2) the overlapping cytokines plus those unique to that cohort, resulting in ten sets of factors. As a sensitivity analysis, we repeated these using PCA. We assessed the similarity of the axes via the correlation between the loadings for the inflammaging factor derived in InCHIANTI and the comparable factor derived in the dataset with the same cytokines. To verify factor stability, we replicated FA across subsets within each cohort (the full study population, female subjects only, male subjects only, persons under 65 years of age and persons aged 65 years and over) and computed correlation coefficients between the axis loadings for each. For OA HeLP, we did not compare the over/under age 65 years subgroups as there were only 32 individuals aged 65 years or more.

For each of the four FAs derived in InCHIANTI, we computed individual factor scores using the regression method. For individuals in InCHIANTI, factor scores were computed based on the FAs with (1) 19 cytokines, (2) 16 cytokines overlapping with SLAS, (3) 8 cytokines overlapping with Tsimane and (4) 8 cytokines overlapping with OA HeLP. Correlations between these factor scores are reported. Factor scores for individuals in SLAS, THLHP and OA HeLP were computed using cytokine levels from those datasets and factor loadings derived in InCHIANTI (the aforementioned (2), (3) and (4), respectively). For each cohort, we fit a linear regression of age versus factor score and we report the slope of the best-fit line and its statistical significance, with shading to indicate the 95% confidence interval for this best-fit line. We used logistic regression to assess relationships between factor scores and health outcomes, adjusting for age and BMI (using cubic splines) and sex. When fewer than ten individuals reported having a condition, we adjusted for sex, age and BMI. We report ORs and 95% confidence intervals. Not all health outcomes were available in all datasets. These main analyses used InCHIANTI as the reference population. They were repeated using each of the other three cohorts (SLAS, THLHP and OA HeLP) as the reference population.

We used linear regression to assess the effects of smoking, BMI, eosinophil percent and leukocyte count on inflammaging, adjusted for age (using a cubic spline to account for nonlinear relationships) and sex.

Inclusion and ethics statement All collaborators in this study have fulfilled the authorship criteria required by Nature journals, as their contributions were essential to the design and implementation of the research. Roles and responsibilities were agreed upon before the study. The research was locally relevant and conducted in collaboration with local partners. There were no severe restrictions or prohibitions, and the research posed no risks of stigmatization, discrimination or personal harm to participants. Local and regional research relevant to the study was appropriately cited.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The InCHIANTI, SLAS, THLHP and OA HeLP datasets used in this study are not publicly available due to privacy and ethical restrictions on human health data. Access can be requested from the respective data owners. Both THLHP and OA HeLP adhere to the CARE Principles for Indigenous Data Governance and the FAIR Guiding Principles, ensuring participant sovereignty and ethical data use. Requests for individual-level data require formal applications, with considerations for privacy and community benefits. Requests for SLAS data should be directed to J.P.S.Y. (yeongps@imcb.a-star.edu.sg) and R.H. (pcmrhcm@nus.edu.sg). The cohort datasets are available via https://www.nia.nih.gov/inchianti-study#access (InCHIANTI), https://tsimane.anth.ucsb.edu/data.html (THLHP) and orangaslihealth.org (OA HeLP).

Code availability

All the scripts developed for this study are available via GitHub at https://github.com/cohenaginglab/InflammagingDiversity.

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Author contributions

M.F. and A.A.C. designed the study and wrote the manuscript. M.F., K.T.T., R.L.T., C.D., A.M. and E.G.C. conducted data analysis. L.F., S.B., M.G., B.C.T., H.S.K., J.S., J.E.A., T.S.K., A.J.L., V.V.V., I.J.W., Y.A.L.L., K.S.N., J.P.S.Y., X.L. and R.H. provided access to, and help interpreting, the relevant datasets. All authors contributed to interpreting the data and editing the manuscript. A.A.C., M.G., T.F., M.L. and J.H. conceived of and obtained funding for the larger project of which this study is a part.

Competing interests

A.A.C. is founder and CEO at Oken Health. The other authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to Maximilien Franck or Alan A. Cohen.

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[1]Research Center on Aging, Faculty of Medicine and Health Sciences, University of Sherbrooke, Sherbrooke, Quebec, Canada. [2]Robert N. Butler Columbia Aging Center, Mailman School of Public Health, Columbia University, New York, NY, USA. [3]Department of Biological Sciences, Vanderbilt University, Nashville, TN, USA. [4]Department of Sociology, University of Utah, Salt Lake City, UT, USA. [5]Population Health and Optimal Health Practices Branch, CHU de Québec Research Center, Quebec, Quebec, Canada. [6]Longitudinal Studies Section, Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA. [7]Geriatric Unit, Azienda Sanitaria Firenze, Florence, Italy. [8]Center for Evolution and Medicine, School of Human Evolution and Social Change, Institute of Human Origins, Arizona State University, Tempe, AZ, USA. [9]Economic Science Institute, Argyros College of Business and Economics, Chapman University, Orange, CA, USA. [10]Department of Social and Behavioral Sciences, Toulouse School of Economics, Institute for Advanced Study in Toulouse, Université Toulouse Capitole, Toulouse, France. [11]Department of Anthropology, University of Utah, Salt Lake City, UT, USA. [12]Department of Anthropology and Archaeology, University of Calgary, Calgary, Alberta, Canada. [13]Department of Anthropology, University of New Mexico, Albuquerque, NM, USA. [14]Department of Parasitology, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia. [15]Department of Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia. [16]Institute of Molecular and Cell Biology, Agency for Science, Technology and Research (A*STAR), Singapore, Republic of Singapore. [17]Department of Anatomical Pathology, Singapore General Hospital, Singapore, Republic of Singapore. [18]Department of Microbiology, Singapore General Hospital, Singapore, Republic of Singapore. [19]Duke–NUS Medical School, Singapore, Republic of Singapore. [20]Division of Functional Near Infrared Spectroscopy, Institute for Health Innovation and Technology (iHealthtech), National University of Singapore, Singapore, Republic of Singapore. [21]Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany. [22]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA. [23]Institute of Immunology, University of Tübingen, Tübingen, Germany. [24]Health Sciences North Research Institute, Sudbury, Ontario, Canada. [25]Institute of Biogerontology, Lobachevsky State University, Nizhny Novgorod, Russia. [26]German Center for Cardiovascular Diseases, Partner Site Greifswald, Greifswald, Germany. [27]Univ. Bordeaux, CNRS, Immuno ConcEpT, UMR 5164, Bordeaux, France. [28]Department of Anthropology, University of California Santa Barbara, Santa Barbara, CA, USA. [29]Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY, USA. ✉e-mail: maximilien.franck5@gmail.com; aac2277@cumc.columbia.edu

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Extended Data Table 1 | Associations of the InCHIANTI-derived inflammaging factor with BMI and smoking

Reference population	Cytokines in common with	Target population	N	BMI			Smoking		
				ß	95% CI	*p*	ß	95% CI	*p*
InCHIANTI	-	InCHIANTI	998	0.04	(0.03, 0.06)	<0.0001	0.09	(-0.02, 0.19)	0.10
InCHIANTI	SLAS	InCHIANTI	1023	0.04	(0.03, 0.05)	<0.0001	0.09	(-0.01, 0.19)	0.07
InCHIANTI	SLAS	SLAS	776	0.04	(0.03, 0.06)	<0.0001	0.19	(0.08, 0.30)	0.001
InCHIANTI	THLHP	InCHIANTI	1037	0.04	(0.03, 0.05)	<0.0001	0.13	(0.03, 0.24)	0.01
InCHIANTI	THLHP	THLHP	249	-0.01	(-0.04, 0.03)	0.772	0.02	(-0.27, 0.31)	0.92
InCHIANTI	OA HeLP	InCHIANTI	1122	0.04	(0.03, 0.05)	<0.0001	0.11	(0.01, 0.21)	0.03
InCHIANTI	OA HeLP	OA HeLP	341	0.04	(0.02, 0.06)	0.0002	-0.12	(-0.37, 0.13)	0.34
Reference population	**Cytokines in common with**	**Target population**	**N**	**Eosinophilia**			**Leukocytosis**		
				ß	**95% CI**	***p***	**ß**	**95% CI**	***p***
				Crude association					
InCHIANTI	THLHP	THLHP	391 / 394	0.23	(0, 0.46)	0.05	0.34	(0.15, 0.54)	0.001
InCHIANTI	OA HeLP	OA HeLP	245 / 244	0.19	(-0.08, 0.46)	0.17	0.76	(0.48, 1.03)	<0.0001
				Adjusted for BMI and smoking					
InCHIANTI	THLHP	THLHP	221 / 221	0.00	(-0.29, 0.30)	0.99	0.30	(0.04, 0.56)	0.020
InCHIANTI	OA HeLP	OA HeLP	234 / 233	0.18	(-0.09, 0.45)	0.20	0.75	(0.47, 1.03)	<0.0001

All models are adjusted for sex and for age as a cubic spline. BMI and smoking coefficients are also adjusted for smoking and BMI respectively. Eosinophilia and leukocytosis are additionally adjusted as indicated. *Smoking in InCHIANTI and SLAS is a 1 if current or former smoker. Smoking in OA HeLP is a 1 if sometimes or every day smoke a cigarette or loose-leaf tobacco. Smoking in Tsimane is 1 if smoker or pack years > 0 (n=256). P-values are based on a 2-sided Wald test.

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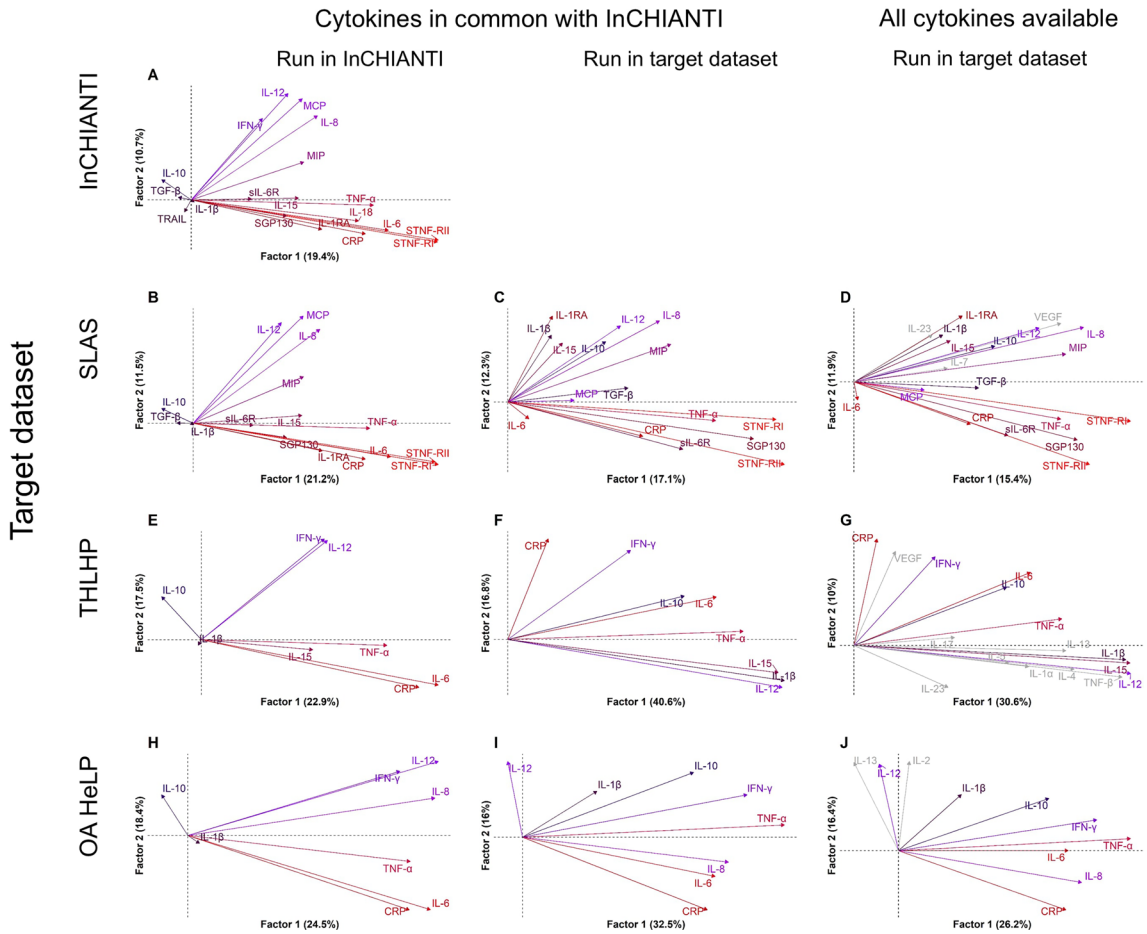
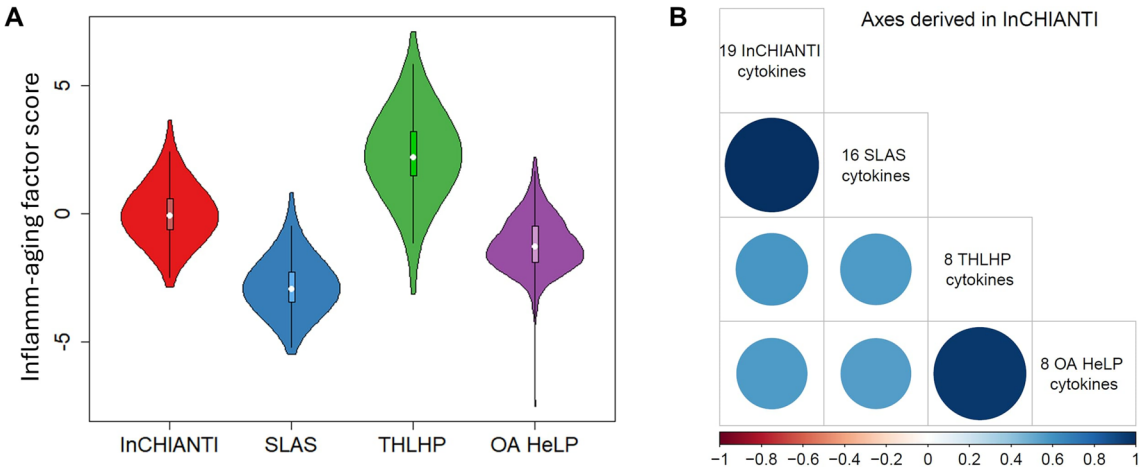


Extended Data Fig. 1 | Axis structure of cytokines run with PCA rather than FA. Biplots show the associations of cytokines with the first two axes run in different datasets and with different sets of cytokines. The colors of each arrow are reproduced from panel **A** across panels to facilitate comparison, with red indicating strong association with the first factor in panel **A**, purple with the second factor, and black with the origin (no association). A color pattern similar to panel **A** thus indicates a similar axis structure. The first column (panels **A**, **B**, **E**, and **H**) shows analyses run in InCHIANTI, but with subsets of cytokines that overlap with those available, respectively, in the full InCHIANTI set (**A**), SLAS (**B**), THLHP (**E**), and OA HeLP (**H**). The second column (panels **C**, **F**, and **I**) shows the axis structure of the same cytokines as in column 1 (panels **B**, **E**, and **H**, respectively), except run in the target datasets, not InCHIANTI. The third column (panels **D**, **G**, and **J**) replicates the analysis in the second column but adding in the cytokines not measured in InCHIANTI (light grey).

https://doi.org/10.1038/s43587-025-00888-0



Extended Data Fig. 2 | Properties of the inflammaging axis derived in InCHIANTI. A. Violin plots of the distributions of the inflammaging factors scores calculated in each respective population, based on the factor loadings derived from InCHIANTI (see Methods). Note that it is not clear whether these scores are directly comparable given the different assays used for each dataset; nonetheless, high scores in THLHP is consistent with previous reporting of high levels of inflammatory and immune markers in the Tsimane. Number of biological replicates: InCHIANTI (1041), SLAS (941), THLHP (536), OA HeLP (358). The white circle is the median and the surrounding rectangle indicates the 25th-75th percentile or interquartile range (IQR). Vertical black lines (whiskers) show 1.5*IQR, and the plots extend to the maxima/minima of the smoothed kernel density estimate of the data distribution. **B**. Pairwise correlations among the scores of the inflammaging axis in InCHIANTI when derived from different sets of cytokines: the original set of 19, the 16 that overlap with SLAS, the eight that overlap with THLHP, and the eight that overlap with OA HeLP. All are significant at $p < 0.0001$.

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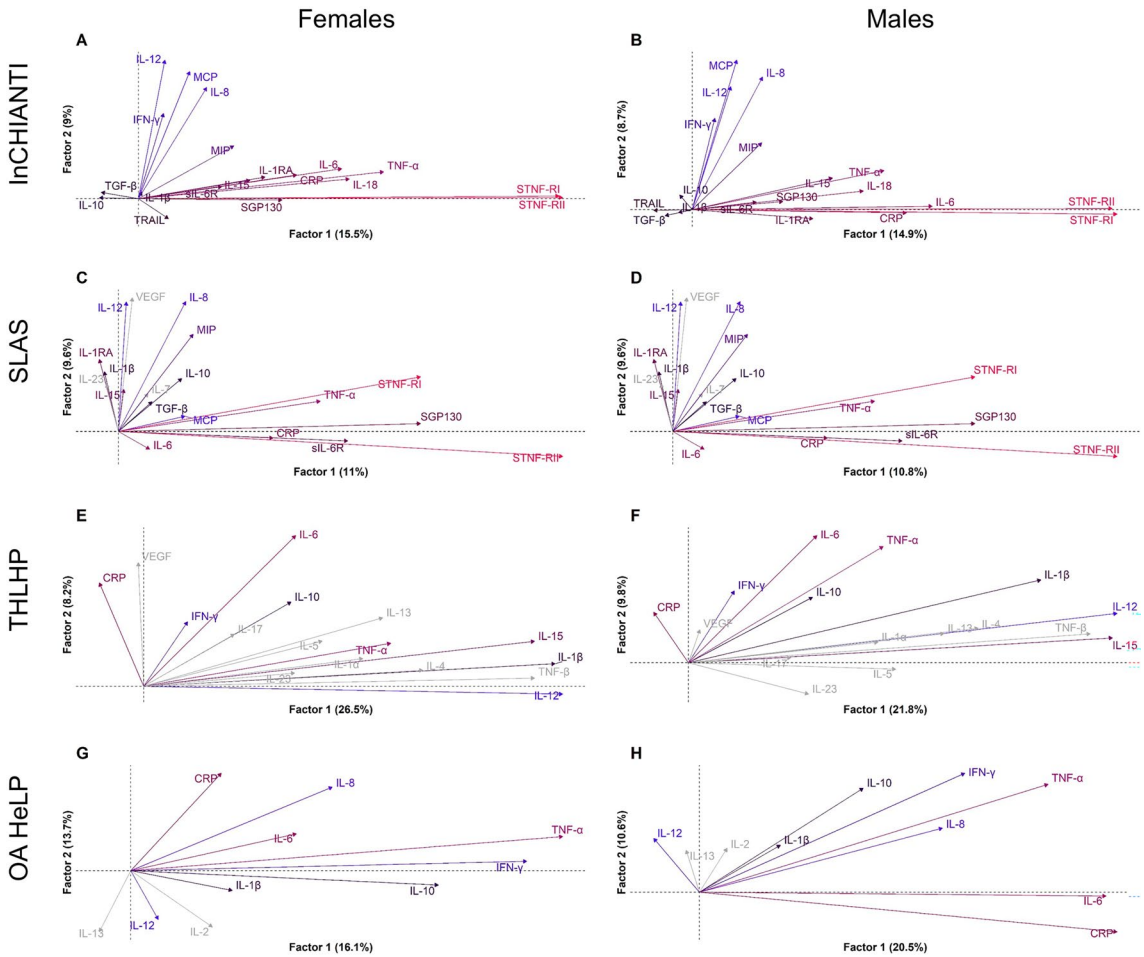

Extended Data Fig. 3 | Sex-specific biplots of factor scores in each dataset. Biplots show the associations of cytokines with the first two factors run in different datasets and by sex with the full set of cytokines available in that dataset. The colors of each arrow are reproduced from Fig. 2a across panels to facilitate comparison, with red indicating strong association with the first factor in Fig. 2a, purple with the second factor, and black with the origin (no association). Similar color patterns between female subjects (**A**, **C**, **E**, and **G**) and male subjects (**B**, **D**, **F**, and **H**) thus indicates a similar axis structure. Note that the structure is nearly identical for InCHIANTI (**A**, **B**) and SLAS (**C**, **D**), quite similar for THLHP (**E**, **F**), and somewhat more distinct for OA HeLP (**G**, **H**), where the sample size is smaller and structure is estimated with greater error.

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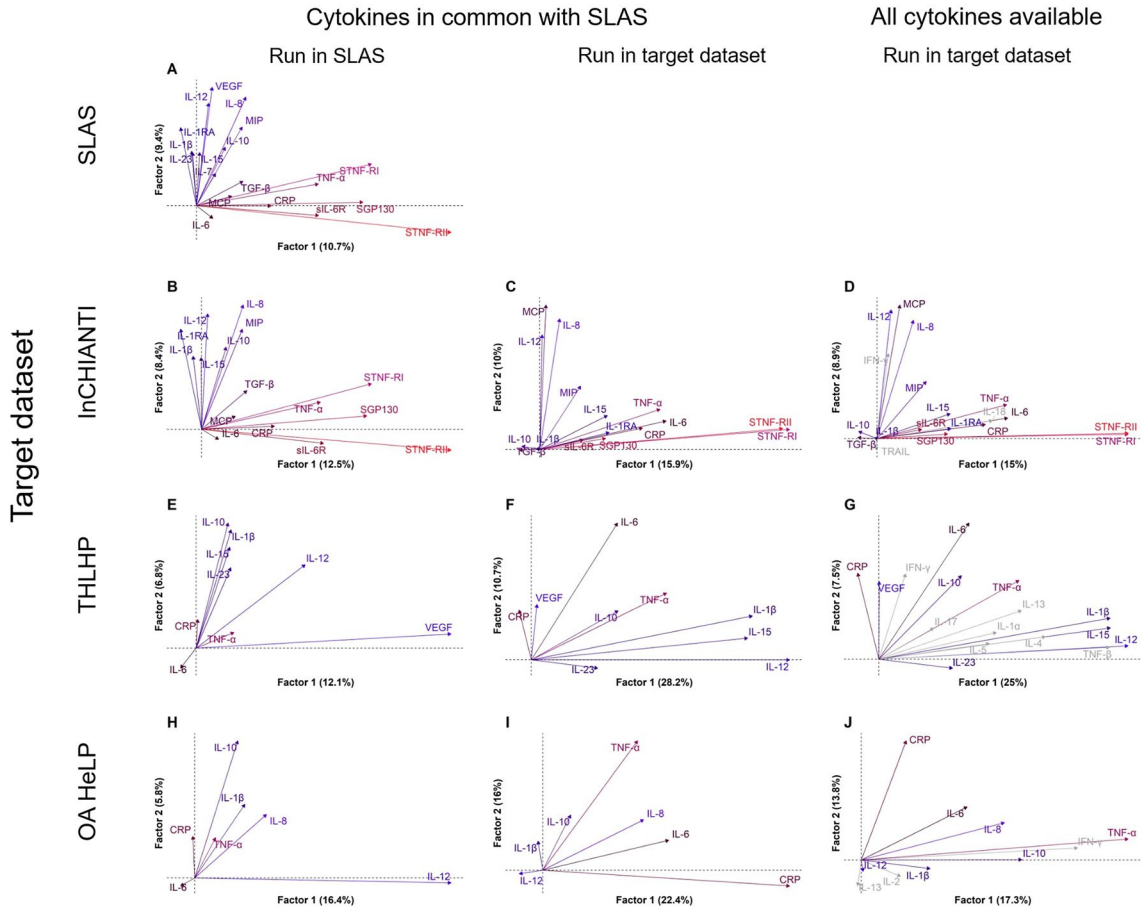

Extended Data Fig. 4 | Replication of the SLAS factor structure across populations. Biplots show the associations of cytokines with the first two factors run in different datasets and with different sets of cytokines. The colors of each arrow are reproduced from panel **A** across panels to facilitate comparison, with red indicating strong association with the first factor in panel **A**, purple with the second factor, and black with the origin (no association). A color pattern similar to panel **A** thus indicates a similar axis structure. The first column (panels **A**, **B**, **E**, and **H**) shows analyses run in SLAS, but with subsets of cytokines that overlap with those available, respectively, in the full SLAS set (**A**), InCHIANTI (**B**), THLHP (**E**), and OA HeLP (**H**). The second column (panels **C**, **F**, and **I**) shows the axis structure of the same cytokines as in column 1 (panels **B**, **E**, and **H**, respectively), except run in the target datasets, not SLAS. The third column (panels **D**, **G**, and **J**) replicates the analysis in the second column but adding in the cytokines not measured in SLAS (light grey). Correlation coefficients between columns 1 and 2 show the Spearman correlations of the loadings between the indicated panels.

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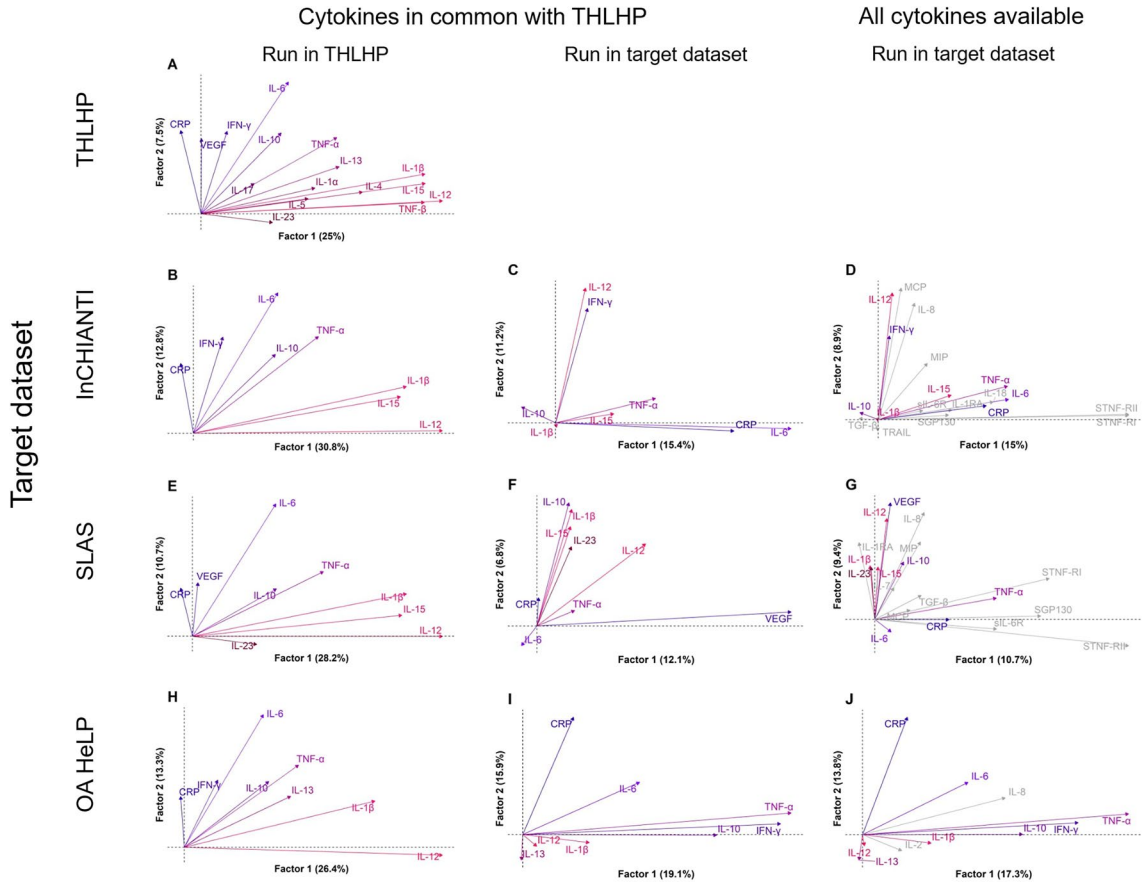

Extended Data Fig. 5 | Replication of the THLHP factor structure across populations. Biplots show the associations of cytokines with the first two factors run in different datasets and with different sets of cytokines. The colors of each arrow are reproduced from panel **A** across panels to facilitate comparison, with red indicating strong association with the first factor in panel **A**, purple with the second factor, and black with the origin (no association). A color pattern similar to panel **A** thus indicates a similar axis structure. The first column (panels **A**, **B**, **E**, and **H**) shows analyses run in THLHP, but with subsets of cytokines that overlap with those available, respectively, in the full THLHP set (**A**), InCHIANTI (**B**), SLAS (**E**), and OA HeLP (**H**). The second column (panels **C**, **F**, and **I**) shows the axis structure of the same cytokines as in column 1 (panels **B**, **E**, and **H**, respectively), except run in the target datasets, not THLHP. The third column (panels **D**, **G**, and **J**) replicates the analysis in the second column but adding in the cytokines not measured in THLHP (light grey). Correlation coefficients between columns 1 and 2 show the Spearman correlations of the loadings between the indicated panels.

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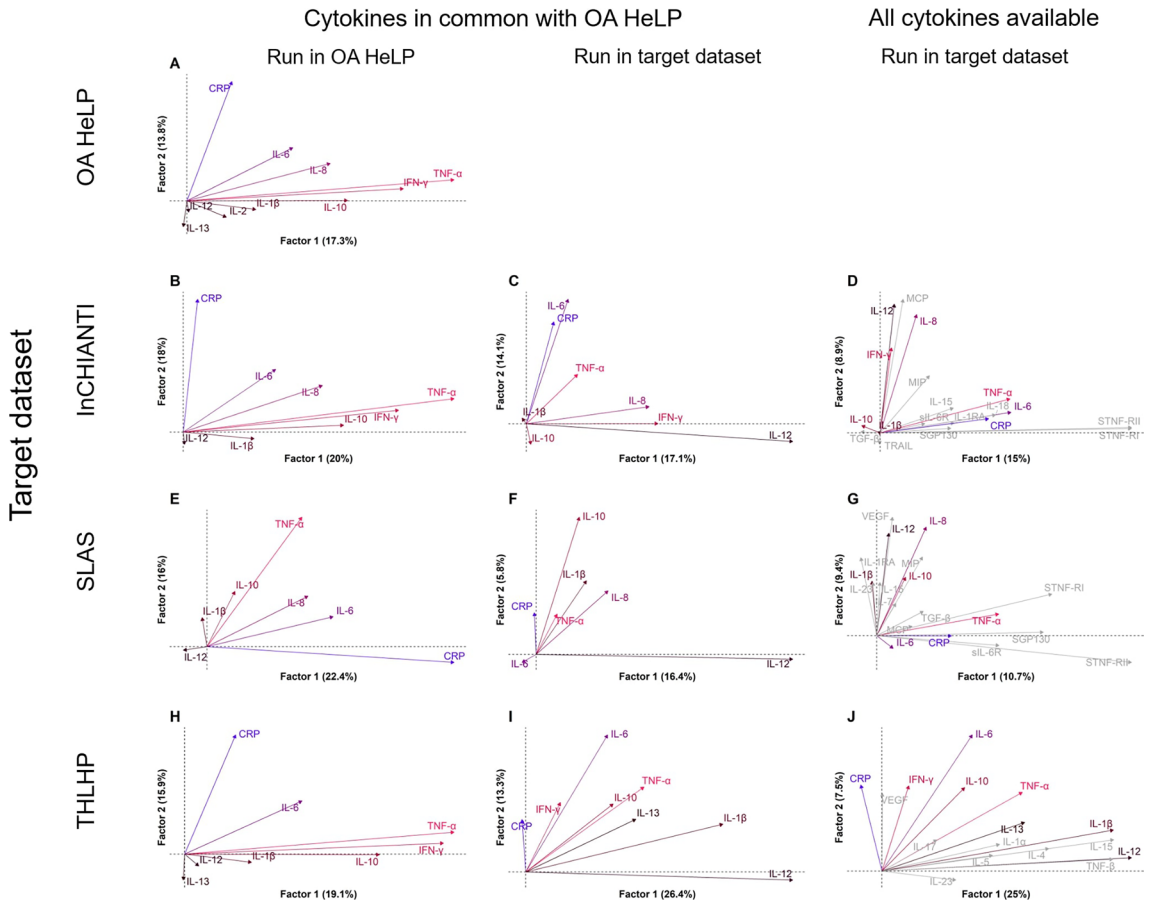

Extended Data Fig. 6 | Replication of the OA HeLP factor structure across populations. Biplots show the associations of cytokines with the first two factors run in different datasets and with different sets of cytokines. The colors of each arrow are reproduced from panel **A** across panels to facilitate comparison, with red indicating strong association with the first factor in panel **A**, purple with the second factor, and black with the origin (no association). A color pattern similar to panel **A** thus indicates a similar axis structure. The first column (panels **A**, **B**, **E**, and **H**) shows analyses run in OA HeLP, but with subsets of cytokines that overlap with those available, respectively, in the full OA HeLP set (**A**), InCHIANTI (**B**), SLAS (**E**), and THLHP (**H**). The second column (panels **C**, **F**, and **I**) shows the axis structure of the same cytokines as in column 1 (panels **B**, **E**, and **H**, respectively), except run in the target datasets, not OA HeLP. The third column (panels **D**, **G**, and **J**) replicates the analysis in the second column but adding in the cytokines not measured in OA HeLP (light grey). Correlation coefficients between columns 1 and 2 show the Spearman correlations of the loadings between the indicated panels.

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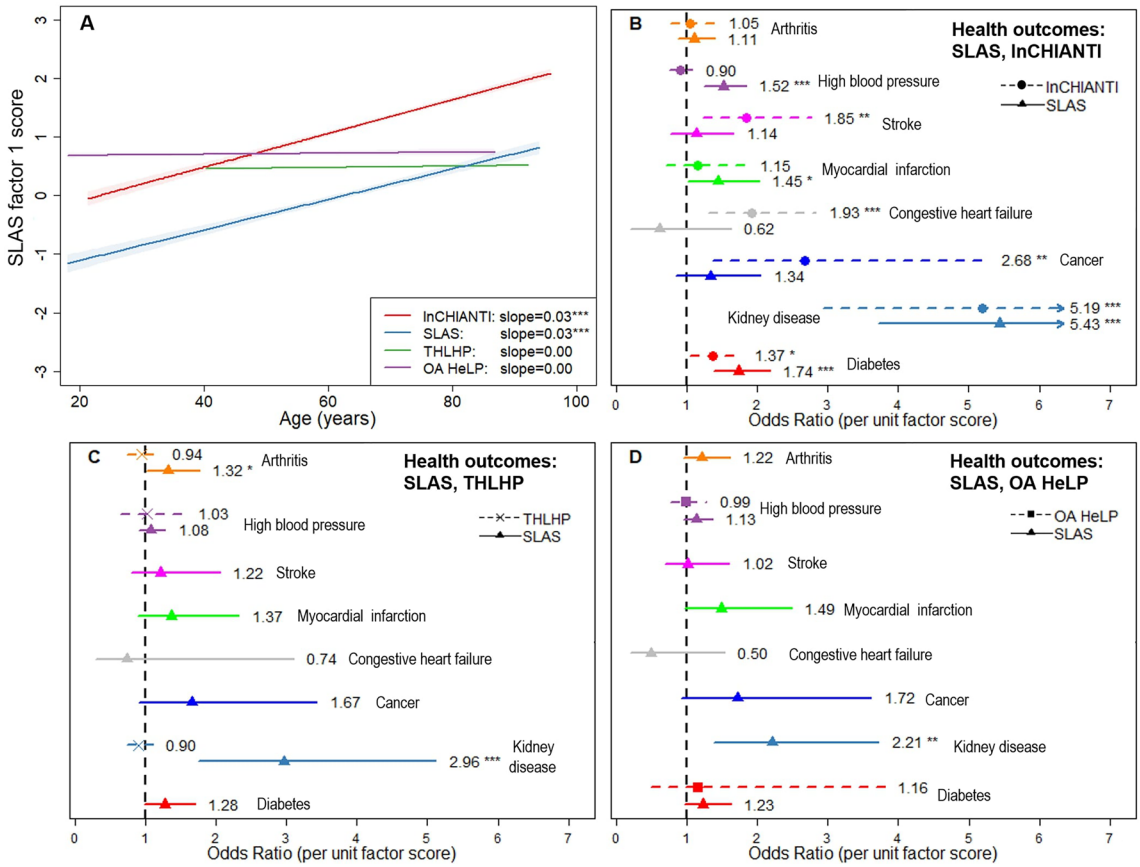

Extended Data Fig. 7 | Associations of the first SLAS factor with age and health outcomes. A. Associations between the SLAS factors derived in Extended Data Figs. 4A, B, E, and H with age, when applied in the respective datasets. The shaded region is a 95% confidence interval for the best-fit lines shown. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$ based on a 2-sided Wald test. **B.** Comparison of prediction of health outcomes in InCHIANTI and SLAS using the first SLAS factor derived in Extended Data Fig. 4B. **C.** Comparison of prediction of health outcomes in SLAS and THLHP using the first SLAS factor derived in Extended Data Fig. 4E. Not all outcomes are available in THLHP. **D.** Comparison of prediction of health outcomes in SLAS and OA HeLP using the first SLAS factor derived in Extended Data Fig. 4H. Not all outcomes are available in OA HeLP. For panels **B**–**D**, the point indicates the estimated odds ratio and the line the 95% confidence interval; the vertical line indicates no effect. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$ based on a 2-sided Wald test. Odds ratios are scaled per unit factor score. Because factor score ranges are 6+ within populations (cf. Extended Data Fig. 2A), an odds ratio of 1.5 translates into at least $1.56 = 11.4$ across the range of values in the populations. Note that different ORs for SLAS in panels **B**, **C**, and **D** are due to different versions of the factor using overlapping biomarker sets with the other datasets. Number of biological replicates: InCHIANTI (1041), SLAS (941), THLHP (536), OA HeLP (358). Supplemental Table S1 details availability of health outcomes by dataset.

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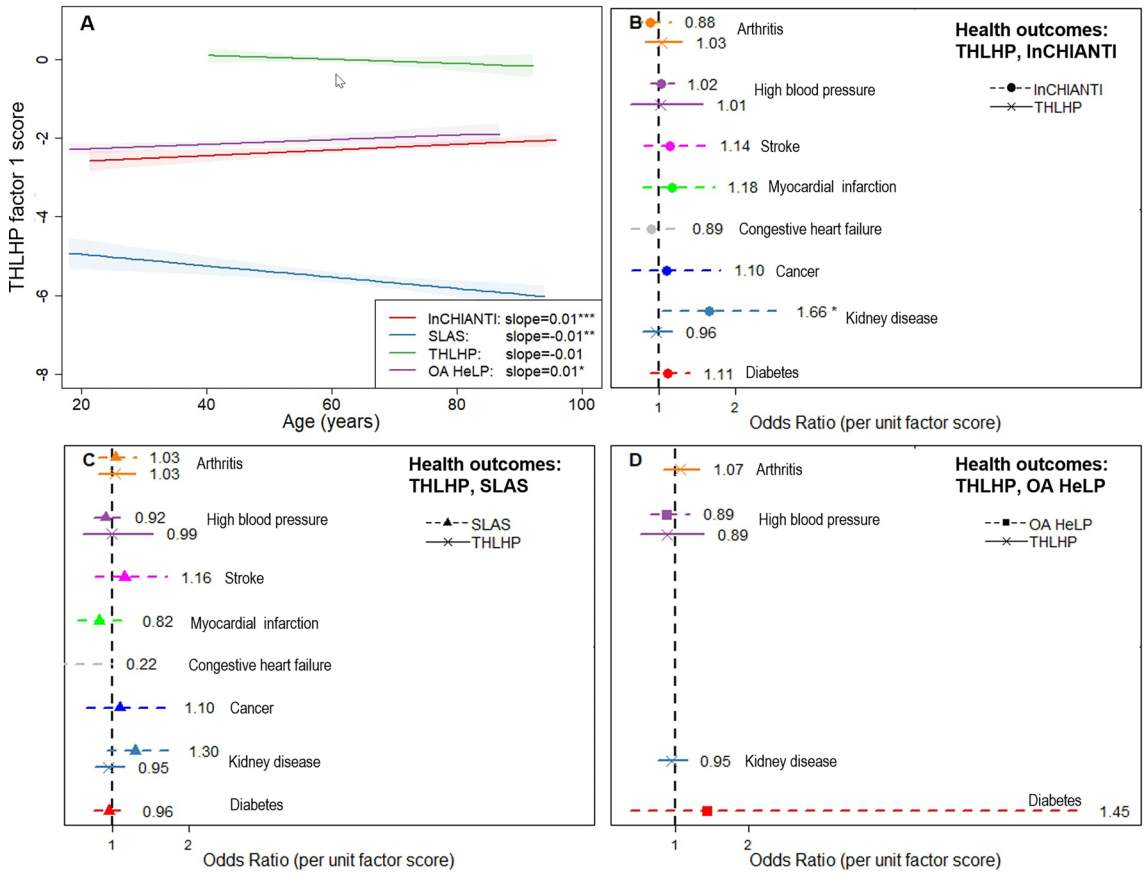

Extended Data Fig. 8 | Associations of the first THLHP factor with age and health outcomes. A. Associations between the THLHP factors derived in Extended Data Fig. 5A, B, E, and H with age, when applied in the respective datasets. The shaded region is a 95% confidence interval for the best-fit lines shown. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$ based on a 2-sided Wald test. **B**. Comparison of prediction of health outcomes in InCHIANTI and THLHP using the first THLHP factor derived in Extended Data Fig. 5B. **C**. Comparison of prediction of health outcomes in SLAS and THLHP using the first THLHP factor derived in Extended Data Fig. 5E. Not all outcomes are available in THLHP. **D**. Comparison of prediction of health outcomes in THLHP and OA HeLP using the first THLHP factor derived in Extended Data Fig. 5H. Not all outcomes are available in OA HeLP. For panels **B**–**D**, the point indicates the estimated odds ratio and the line the 95% confidence interval; the vertical line indicates no effect. *: $p < 0.05$ based on a 2-sided Wald test. Odds ratios are scaled per unit factor score. Because factor score ranges are 6+ within populations (cf. Extended Data Fig. 2A), an odds ratio of 1.5 translates into at least $1.56 = 11.4$ across the range of values in the populations. Note that different ORs for THLHP in panels **B**, **C**, and **D** are due to different versions of the factor using overlapping biomarker sets with the other datasets. Number of biological replicates: InCHIANTI (1041), SLAS (941), THLHP (536), OA HeLP (358). Supplemental Table S1 details availability of health outcomes by dataset.

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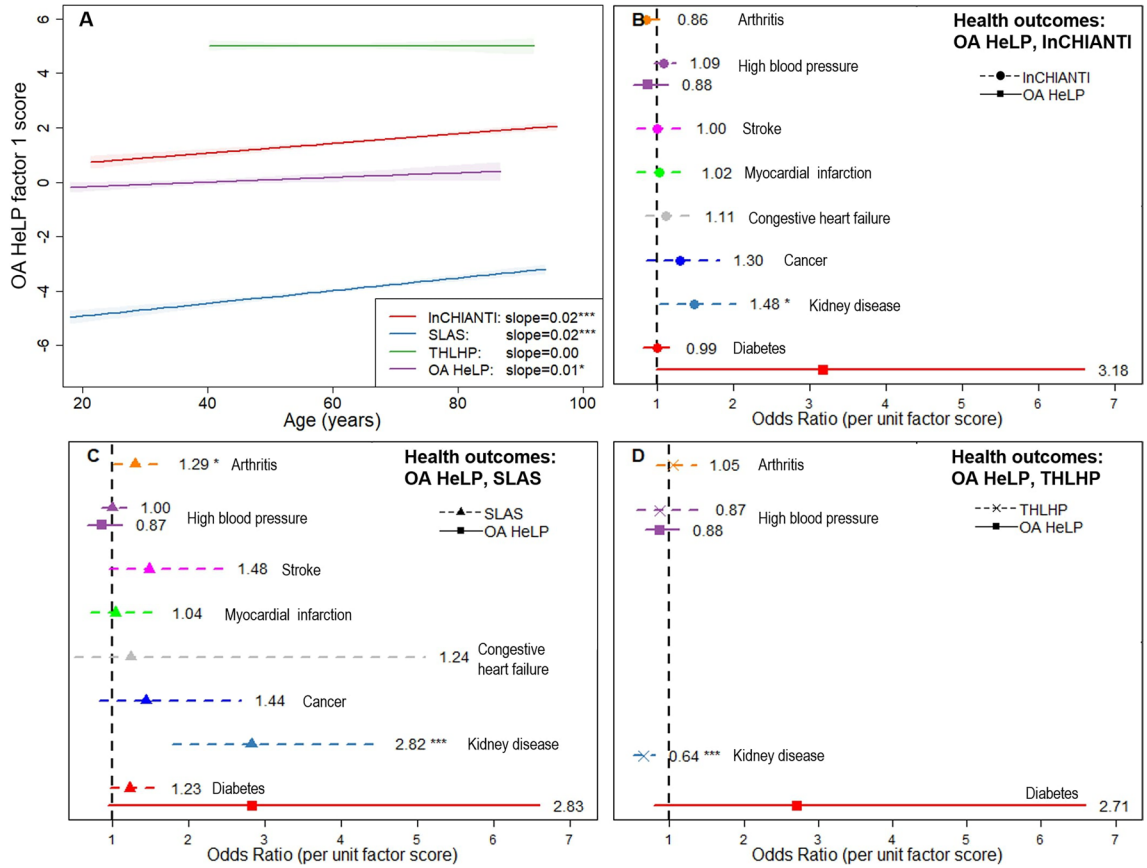

Extended Data Fig. 9 | Associations of the first OA HeLP factor with age and health outcomes. A. Associations between the OA HeLP factors derived in Extended Data Fig. 6A, B, E, and H with age, when applied in the respective datasets. The shaded region is a 95% confidence interval for the best-fit lines shown. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$ based on a 2-sided Wald test. B. Comparison of prediction of health outcomes in InCHIANTI and OA HeLP using the first OA HeLP factor derived in Extended Data Fig. 6B. **C**. Comparison of prediction of health outcomes in OA HeLP and SLAS using the first OA HeLP factor derived in Extended Data Fig. 6E. Not all outcomes are available in THLHP. **D**. Comparison of prediction of health outcomes in THLHP and OA HeLP using the first SLAS factor derived in Extended Data Fig. 6H. Not all outcomes are available in OA HeLP. For panels **B**–**D**, the point indicates the estimated odds ratio and the line the 95% confidence interval; the vertical line indicates no effect. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$ based on a 2-sided Wald test. Odds ratios are scaled per unit factor score. Because factor score ranges are 6+ within populations (cf. Extended Data Fig. 2A), an odds ratio of 1.5 translates into at least $1.56 = 11.4$ across the range of values in the populations. Note that different ORs for OA HeLP in panels **B**, **C**, and **D** are due to different versions of the factor using overlapping biomarker sets with the other datasets. Number of biological replicates: InCHIANTI (1041), SLAS (941), THLHP (536), OA HeLP (358). Supplemental Table S1 details availability of health outcomes by dataset.

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Corresponding author(s): Alan Arthur Cohen & Maximilien Franck

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☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
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☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used for data collection, as the study is based on secondary analysis of previously collected datasets.
Data analysis	Data analysis was conducted using R software version 4.3.2 and its associated packages, including the 'factanal' function for factor analysis and the 'miWQS' package version 0.4.4 for multiple imputation.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The InCHIANTI, SLAS, THLHP, and OA HeLP datasets used in this study are not publicly available due to privacy and ethical restrictions on human health data. Access can be requested from the respective data owners. Both THLHP and OA HeLP adhere to the CARE Principles for Indigenous Data Governance and the FAIR Guiding Principles, ensuring participant sovereignty and ethical data use. Requests for individual-level data require formal applications, with considerations for privacy and

community benefits. SLAS data may be available upon appropriate request from JPSY and RH.

All the scripts developed for this study are available at https://github.com/cohenaginglab/InflammagingDiversity

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Sex was considered as a biological variable in the study. Data were disaggregated by sex, and analyses were conducted separately for males and females where relevant (Figure 3, panel K). Sex was determined based on self-reporting from participants in each of the datasets used (InCHIANTI, SLAS, THLHP, and OA HeLP). Sex-based analyses were conducted, including sex-specific factor analysis (Supplementary Figure S3).
Reporting on race, ethnicity, or other socially relevant groupings	Race/ethnicity was inferred from geographic and cultural background, as defined by the respective cohort studies. Participants were thus grouped by cohort which correspond to geographical and cultural background: Italians (InCHIANTI), Singaporeans (SLAS), Tsimane (THLHP), and Orang Asli (OA HeLP). These categorizations were used to explore the potential influence of different environmental, lifestyle, and cultural factors on inflammaging across diverse populations. Where relevant, we controlled for potential confounders such as age, sex, and BMI in the analysis.
Population characteristics	The study included individuals from four different populations: InCHIANTI (Italy), SLAS (Singapore), THLHP (Tsimane, Bolivia), and OA HeLP (Orang Asli, Malaysia). Participants ranged in age from young adults to older individuals (with a particular focus on those aged 55+ in industrialized cohorts). Health data included the presence or absence of common age-related diseases (e.g., cardiovascular disease, diabetes, hypertension) and inflammatory markers.
Recruitment	Participants in the InCHIANTI, SLAS, THLHP, and OA HeLP studies were recruited through various community-based sampling methods. InCHIANTI recruited subjects from population-based registries and SLAS through a door-to-door census. In the THLHP, participants were recruited from Tsimane villages through a combination of village-based epidemiological data collection and healthcare efforts. The study involved regular person-visits by project physicians to address a wide range of medical needs. Orang Asli participants were recruited through community engagement, with permission from leaders (penghulu or tok batin) and public meetings with community advisory committees. Recruitment strategies aimed to achieve a representative sample for each population. Potential selection bias may arise from non-response or differing levels of participation across demographic groups, but these biases are unlikely to significantly affect the results.
Ethics oversight	Written informed consent was obtained for all study participants in all cohorts. THLHP data collection was approved by the University of New Mexico (#07-157) and the University of California, Santa Barbara (#3-21-0652) Human Subjects Review Committees. For the Tsimane participants, written informed consent was provided after procedures and risks were explained in their native language, with approvals from each village and the Tsimane Government (Gran Consejo). OA HeLP data collection was approved by the Medical Review and Ethics Committee of the Malaysian Ministry of Health (protocol ID: NMRR-20-2214-55565), the Malaysian Department of Orang Asli Development (permit ID: JAKOA.PP.30.052 JLD 21 (98)), and the Institutional Review Board of Vanderbilt University (protocol ID: 212175). Community-level approval was obtained prior to recruitment, and written informed consent was obtained from all participants. SLAS data collection was approved by the National University of Singapore Institutional Review Board (Ref: L04-140C). Participants in SLAS provided written informed consent. InCHIANTI data collection was approved by the Ethical Committee at INRCA, Ancona (protocol 14/CE, 28 February 2000) and FU1 (protocol 45/01, 16 January 2001); participants provided written informed consent. Secondary analysis was approved by the University of Sherbrooke Ethics Board (Ref: 2019-2657) and Columbia University Medical Center's IRB (AAAU5622).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No formal sample-size calculation was performed. Instead, we included as many participants as possible from each cohort based on the availability of the relevant variables we used (so biomarkers). This approach ensured maximum use of the available data while maintaining sufficient variability for robust statistical analyses.
Data exclusions	Biomarkers that were not common with the InCHIANTI dataset were not included in the main analyses. Additionally, participants from the THLHP cohort with excessive missing data were excluded from the analysis. These exclusions were pre-established to ensure comparability with the InCHIANTI cohort and maintain the integrity of the statistical analyses.
Replication	This study is a replication of a previous study in one cohort across four cohorts. In addition, we replicate within each cohort by stratifying by

Replication	sex and age. Lastly, two independent team members (MF and KT) replicated all the statistical analyses to ensure the robustness and reproducibility of the findings.
Randomization	Randomization was not applicable, as this was an observational study with population-based cohorts. However, covariates such as age, sex, and BMI were controlled for in the analyses.
Blinding	Blinding was not applicable, as this was an observational study, and participants were selected based on predetermined inclusion criteria in each cohort.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
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☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Plants

Seed stocks	Not applicable.
Novel plant genotypes	Not applicable.
Authentication	Not applicable.