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Identification of genes shared between sedentary behaviour and inflammation: a bivariate genetic correlation analysis

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Abstract
Sedentary behaviour is associated with increased risk of several chronic conditions and all-cause mortality. Leisure screen time (LST) represents a substantial component of sedentary behaviour and is linked with higher levels of inflammation and increased body mass index (BMI), which in turn predispose to different disorders and negative health outcomes, both in the general population as well as in people with high levels of physical activity. Sedentary behaviour and inflammation are complex traits characterized by the interaction between genetic and environmental factors. While some of the genetic factors underlying LST have been suggested to be shared with body composition, to our knowledge the pleiotropy between LST and inflammation has not been investigated. In this study, we used global and local genetic correlation to identify genetic determinants shared between LST and two inflammatory markers, C-reactive protein (CRP) and interleukin 6 (IL6), using large genomic datasets. We compare results obtained with the definition of genomic loci based on the genome partitioning algorithm proposed in LAVA and a modified version in which loci are defined based on gene coordinates. We found a significant global genetic correlation between LST and CRP ($r_g = 0.37$, p= 1.6E-34) or IL6 ($r_g = 0.41$, $p = 1.1$E-08) and identified several genes shared between LST and inflammatory markers, dissecting loci for which the association was mediated by, or independent from, BMI. Our results provide novel knowledge on shared genetic determinants between sedentary behaviour and inflammation and suggest that different definitions of genomic loci can allow to obtain complementary information when using local genetic correlation analysis.

Keywords GWAS · Leisure screen time · Inflammation · Sedentary time · Physical activity

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1 Introduction

Sedentary time represents a serious public health problem, being associated with increased risk of several chronic conditions and all-cause mortality (Ku et al. 2018). Nonetheless, a sedentary lifestyle is increasingly prevalent among both adults and adolescents (Mclaughlin et al. 2020). In fact, in the last decades, the levels of physical activity have gradually decreased, especially in the most urbanized countries of the world, with substantial repercussion on health (Blair 2009). The impact of sedentary behaviour on the onset of diseases can be compared to the effects of smoking, and impacts on a wide variety of conditions, from cardiometabolic illness to mental health (Aaltonen et al. 2010; den Hoed et al. 2013). Sedentary behaviour is also linked with chronic low-grade inflammation and higher circulating levels of inflammatory markers (Henson et al. 2013), which in turn have been associated with increased risk of disorders that represent leading causes of disability and mortality, including cardiovascular, metabolic and neurodegenerative disorders (Furman et al. 2019).

Leisure screen time (LST) is often used as a marker of total sedentary time, since sitting in front of electronic screens represents one of the main sedentary behaviours. Higher levels of screen time have been associated with lower fitness as well as with a wide range of health conditions such as cardiometabolic disorders (Nagata et al. 2023), gastrointestinal disorders (Chen et al. 2024) or psychiatric traits (Zhang et al. 2023). Digital country development is positively correlated with sitting time (Moreno-Llamas et al. 2020), and it is therefore probable that LST will continue to increase in the next few years, due to the advancement and increased availability of digital technology (Proper et al. 2011).

A longer LST has been suggested to represent a health risk factor not only for people who are generally not active, but also for people with high levels of physical activity and even for athletes, who spend significantly more time in sedentary behaviour compared with the general population, exceeding the average sedentary time by almost 80 min per day based on a recent systematic review, possibly to compensate training-related energy expenditure (Franssen et al. 2022). While to date it is still unclear how much physical activity performed with high levels of intensity might counterweight the negative repercussions of sedentary behaviour, available studies suggest that a higher LST exposes to changes in body composition measures also people engaged in high levels of physical activity (Júdice et al. 2022).

Sedentary behaviour and chronic inflammation represent complex phenotypes, i.e. phenotypes characterized by an hereditary component that interacts with environmental factors (Wang et al. 2022). The hereditary component of complex traits generally comprises the contribution of multiple genetic variants with small effect sizes, and can be investigated with genome-wide association studies (GWAS). GWAS systematically analyzes millions of genetic variations across the genome to identify genetic variants significantly associated with a trait (McCarthy et al. 2008), providing insights on the underlying biological mechanisms. In particular, GWAS allows to study single nucleotide polymorphisms (SNP), i.e. the most common type of genetic variation. It has been shown that several genes are related to

more than one phenotype, a phenomenon known as pleiotropy (Chesmore et al. 2018). The identification of genetic markers shared between two traits can be leveraged to increase our understanding of both traits and underlying biological mechanisms (Chesmore et al. 2018). Among the first statistical methods developed to investigate the genetic relationships between two traits, linkage-disequilibrium score regression (LDSC) allows to measure the global genetic correlation between different phenotypes, considering the average of the shared signals across the genome, including the contribution of genetic variants that do not reach genome-wide significance (Bulik-Sullivan et al. 2015a, b). Using this approach, Wang and colleagues showed that LST is significantly positively correlated with adiposity-related traits such as body mass index and body fat percentage, as well as with different neuropsychiatric disorders, while the genetic correlation between LST and circulating levels of inflammatory markers was not investigated (Wang et al. 2022). Global genetic correlation analysis only considers the average of the signals shared between two phenotypes across the genome. On the other hand, recently developed approaches such as Local Analysis of [co]Variant Association (LAVA) (Werme et al. 2022) can allow to obtain relevant information in case genetic signals shared between two or more traits are confined to specific genomic regions or present opposite directions at different loci. In addition, while most other methods for local genetic correlation analysis are restricted to two traits, LAVA allows to conduct partial correlation analysis. For these reasons, LAVA has been widely used to investigate shared genetic determinants between traits such as cardiovascular, metabolic and neuropsychiatric traits (Nievergelt et al. 2024; Adewuyi et al. 2024; Galimberti et al. 2024). However, to our kwowledge, this approach has not been used to date to identify genomic loci shared between LST and other traits. In the method proposed by Werme and colleagues, the genome is partitioned in 2,495 independent loci through an approach that minimizes linkage disequilibrium (LD) between loci (Werme et al. 2022). Therefore, each genomic locus contains multiple genes.

In this study, for the first time we conducted analyses aimed at dissecting shared genetic determinants between LST and levels of circulating inflammatory markers. To this aim, we conducted global and local genetic correlation analysis on the largest available GWAS datasets on LST and two widely studied inflammatory markers, i.e., C-reactive protein (CRP) and interleukin 6 (IL6). Beside the traditional local genetic correlation approach based on the partitioning of the genome in large genomic loci, in Sect. 2 we propose a definition of genomic loci based on genes start and stop coordinates, to identify specific genes shared between the two phenotypes of interest. In Sect. 3, using these complementary approaches, we demonstrate substantial shared genetic heritability between LST and levels of inflammatory markers, and identify specific genes implicated in these phenotypes. In addition, we dissect between loci specifically shared between LST and inflammatory markers and loci for which this association is mediated by body mass index (BMI). In Sect. 4 we discuss potential implications of our results and present potential future developments of this work.

2 Methods

2.1 Genome-wide association scan datasets

We conducted the analyses on the largest publicly available GWAS summary statistics datasets for LST and circulating levels of the inflammatory markers CRP and IL6. All GWAS datasets included only participants of European origin and reported variants on the hg19 mapping. Self-reported LST (i.e. the time spent viewing a TV or PC screen during leisure time), which represents a proxy of sedentary behaviour during leisure time, was assessed in up to 526,725 individuals from UK Biobank and other cohorts as described in Wang et al. (2022). The dataset included 19,742,826 autosomal SNPs. GWAS summary statistics for serum CRP levels were obtained for up to 427,367 UK Biobank participants and 575,531 Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium participants (Said et al. 2022). The GWAS dataset for plasma IL6 levels was produced in the framework of the UK Biobank Pharma Proteomics Project in 34,557 UK Biobank participants (Sun et al. 2023). The CRP and IL6 GWAS datasets included 9,973,021 and 13,999,284 autosomal SNPs, respectively. GWAS summary statistics for BMI for up to 806,834 individuals were obtained from GIANT consortium and UK Biobank and included 27,358,245 autosomal SNPs (Pulit et al. 2019) For all GWAS datasets, ethical approval was obtained by the original GWAS studies and quality control procedures, including imputation, meta-analysis of different cohorts, and adjustment for population stratification, were performed by the original studies (Wang et al. 2022; Said et al. 2022; Sun et al. 2023; Pulit et al. 2019).

Processing of the GWAS datasets with LAVA included the extraction of SNPs common across datasets, alignment of the effect allele to the reference genome (1000 genome European population) and removal of SNPs that could not be aligned. For the analysis conducted on LST and CRP, 9,437,309 SNPs were common to the two datasets. For 1,458,575 SNPs the effect allele could not be aligned to the reference dataset, leading to 7,978,734 autosomal SNPs included in the local genetic correlation analyses. For the analyses conducted on LST and IL6, 12,115,100 SNPs were common to the two datasets. For 1,858,289 SNPs the effect allele could not be aligned to the reference dataset, leading to 10,256,811 autosomal SNPs included in the local genetic correlation analyses.

2.2 Global genetic correlation analysis

We used LDSC to estimate global genetic correlations between LST and genetically-predicted levels of inflammatory markers. The cross-trait LDSC method allows studying the genetic correlation globally, considering the average of the shared signals across the genome, and is robust to sample overlap and population stratification (Bulik-Sullivan et al. 2015a, b). Genetic correlation is computed by normalizing genetic covariance by SNP heritabilities as in Eq. 1:

$$r_g = \frac{\rho_g}{\sqrt{h_1^2 h_2^2}} \quad (1)$$

where ρ_g indicates the genetic covariance and h_i^2 indicates the SNP heritability from study i. Heritability can be defined as the proportion of phenotypic variance that can be explained by the SNPs present in the whole genome (in the case of global genetic correlation analysis) or in a locus (in the case of local genetic correlation analysis). For futher information on heritability in the framework of global genetic correlation analysis please see (Bulik-Sullivan et al. 2015a, b). For each study, GWAS summary statistics were converted into the LDSC format. Quality control procedures included removal of strand-ambiguous and duplicated variants. Alleles were merged with the HapMap3 SNPs using the merge function implemented in LDSC as recommended in the LDSC documentation (https://github.com/bulik/ldsc/wiki/Heritability-and-Genetic-Correlation), while linkage disequilibrium scores were based on 1000 genomes European data.

2.3 Local genetic correlation

Local genetic correlation analysis is conducted on genetic loci rather than being conducted globally, considering the average of the shared signals across the entire genome. Therefore, this method can allow to obtain relevant information in case genetic signals shared between two or more traits are confined to specific genomic regions or present opposite directions at different loci. We used LAVA to test bivariate local genetic correlations between LST and inflammatory markers (Werme et al. 2022). First, local genetic correlation was tested at 2495 loci. In the approach proposed by Werme and colleagues, the genome is divided in 2495 loci defined based on a partitioning algorithm in which LD blocks were generated using the 1000 Genomes phase 3 European data (Werme et al. 2022). However, LAVA can also be used by defining a customized set of loci for which the number of loci, as well as the start and stop position, are defined by the user. We leveraged this function to repeat the analyses using a modified definition of genomic loci, based on start and stop of genes according to the University of California Santa Cruz (UCSC) Genome Browser (Kent et al. 2002). To this aim, we extracted the following information from the UCSC table browser, hg19 mapping for known canonical genes: chromosome, start, stop and gene symbol. From the list of 30,393 genes downloaded from UCSC, 213 transcripts ambiguous or located in multiple chromosomes were excluded. In case of genes with multiple isoforms (n = 1125), the longest isoform was retained and 3934 isoforms were excluded, leading to a total of 26,246 genes included in the analyses and provided at the OSF repository: (https://osf.io/pkxwm). While a genomic locus can contain several genes, thus not allowing to determine which genes might play a more relevant role in the observed signal for local genetic correlation, using gene coordinates allowed to obtain a list of genes for which a significant local genetic correlation between LST and inflammatory markers is suggested. This list of genes can also be used as input for functional enrichment analyses as will be detailed in Sect. 2.4.

To correct for sample overlap, we computed a correlation matrix reporting the phenotypic correlation due to sample overlap using the intercept from cross-trait LDSC (Werme et al. 2022).

For each locus, we converted the marginal SNP effects within the locus to their corresponding joint effects (in order to account for LD between SNPs). To give a brief overview, for any locus and for each quantitative phenotype p, we assume a linear model

$$Y_p = Xa_p + \epsilon_p \tag{2}$$

where Y_p is the standardized phenotype vector, X the standardized genotype matrix (Yang et al. 2011), α_p the vector of standardized joint SNP effects and ϵ_p the vector of normally distributed residuals with mean of 0 and variance η_p^2. Depending on the type of data analyzed, Y values can be continuous (e.g., BMI, blood pressure) or binary (e.g., 0 for controls, 1 for patients). We denote the SNP LD matrix as S = cor(X) and the vector of estimated marginal SNP effects $\hat{\boldsymbol{\beta}}^p$ obtained as the result of linear regression applied considering the SNPs taken one at a time. We obtain the estimated joint effects as $\hat{\boldsymbol{\alpha}}_p = S^{-1}\hat{\boldsymbol{\beta}}^p$, using the genotype reference to compute S. A more detailed explanation, as well as the procedure to obtain the joint SNP effects for binary phenotypes, are reported in the LAVA reference article (Werme et al. 2022). For each locus, the genetic covariance matrix Ω_G is defined as the P × P matrix, where P is the number of phenotypes, representing the goal when estimating the local genetic correlation and N is the original GWAS sample size. The matrix of genetic components Ω, for some specific genetic components $G = Xa$, is obtained by first considering the Eq. 3

$$\Omega_G = cov(G) = \frac{1}{N-1} \times G^T G \tag{3}$$

where G represents the combined genetic effect of all SNPs on the phenotype. Since the initial design matrix can be approximated using principal components (PC) and singular value decomposition (SVD) it is possible to rewrite the above quantity as in Eq. 4

$$\Omega_\delta = cov(\delta) = \frac{\delta^T \delta}{K} = \frac{\Omega_G}{K} \tag{4}$$

where K represents a scaling factor (representing the number of principal components within the locus) and δ the estimated PC projected joint SNP effects. When Ω_δ is expanded as in Eq. 5 it is possible to notice that the elements along the main diagonal (ω_p^2) represent the variance of the genetic component of phenotype p, while the off-diagonal elements ω_{pq} are the covariance of the genetic components for any given couple of phenotypes p and q.

$$\boldsymbol{\Omega}_\delta = \begin{pmatrix} \omega_1^2 & \dots & \omega_{P1} \\ \vdots & \ddots & \vdots \\ \omega_{1P} & \dots & \omega_P^2 \end{pmatrix} \tag{5}$$

Therefore, given each off-diagonal entries we are able to compute the correlations between phenotypes as in Eq. 6

$$\rho_{pq} = \frac{\omega_{pq}}{\sqrt{\omega_p^2} \times \sqrt{\omega_q^2}} \tag{6}$$

This quantifies the extent to which two phenotypes share genetic determinants within a certain genomic locus. Consequently, it indicates the extent to which genetic variations affecting one phenotype also affect another phenotype within that specific genomic locus. Given the above equation, the local R^2 is obtained as ρ_{pq}^2 which represents the proportion of explained variance. The amount of phenotypic variance that can be described by all SNPs in the genome is represented by the SNP-based heritability, thus we can define the local heritability in a similar fashion as the amount of phenotypic variance that can be explained by the SNPs in that locus. Let the adjusted R^2 of the SNP PCs (or heritability) be expressed as in Eq. 7

$$R_{adj}^2 = h^2 = 1 - (1 - R^2)\frac{N-1}{N-K-1}. \tag{7}$$

R^2 represents the unadjusted heritability and is obtained as $R^2 = \frac{var(\hat{G}_p)}{var(Y_p)}$ where var(Y_p) is equal to 1 because of the standardization and var($\hat{G}_p$) = $\hat{\delta}_p^T \hat{\delta}_p$, where $\hat{G}_p$ and $\hat{\delta}_p$ are the sample estimated quantities of G_p and δ_p, respectively. In our study, for each trait, we used the univariate test to test the local heritability within each locus, i.e.the proportion of the variance of a trait that can be explained by the SNPs in that locus. As in previous studies, for these analyses, p-values were adjusted according to Bonferroni based on the number of univariate tests (n = 2,495 loci in the traditional definition of loci, or n = 26,246 genes in our proposed definition of loci based on gene coordinates. The p-values were obtained using a simulation approach based on a noncentral Wishart distribution with a default of 10,000 simulations. This approach also allows to obtain the 95% confidence intervals. Compared with the analyses conducted with the default genome partitioning implemented in LAVA including 2,495 loci, 80 of which showed a significant local heritability for both LST and CRP (3.2%), our proposed definition of loci based on gene coordinates led to a lower percentage of genes with a significant local heritability for both traits (n = 99 genes, 0.4% of the original list of 26,246 genes). The generally shorter span of genomic loci limited to gene coordinates, compared to those defined in the traditional approach, also implies a lower number of SNPs to be represented in these intervals.

For each pair of traits under study (i.e. LST and CRP), for loci for which we identified a significant heritability based on the univariate tests, we computed the bivariate local genetic correlations between the two traits. For bivariate local genetic correlations, *p*-values were adjusted based on the number of conducted bivariate tests for the two traits of interest. Since both sedentary time and inflammation have been suggested to be associated with BMI, it is conceivable that BMI might affect the relationships between the two traits at least at some loci. Therefore, in order to evaluate whether the association between LST and

inflammatory markers was mediated by BMI, we conducted partial correlation analyses adjusted for this trait.

Partial correlation analyses were conducted for all loci or genes showing a significant local heritability for all traits. The conditional partial correlations $\rho_{XY|Z}$ between two phenotypes, e.g. X and Y, based on other phenotypes, $Z = \{Z_1, Z_2, \ldots, Z_n\}$ is obtained as the correlation between the residuals of X and Y from the linear regression models of X with Z and of Y with Z, respectively. Let $G_X = G_Z\beta_X + \epsilon_X$ and $G_Y = G_Z\beta_Y + \epsilon_Y$ then the partial correlation is computed as

$$\rho_{XY|Z} = cor(\epsilon_X, \epsilon_Y) = \frac{\omega_{XY|Z}}{\sqrt{\omega^2_{X|Z}}\sqrt{\omega^2_{Y|Z}}} \tag{8}$$

where $\omega_{XY|Z}$ is the covariance of X and Y with Z, $\omega^2_{X|Z} = \omega^2_X - \Omega_{XY}\Omega_Z^{-1}\Omega_{ZX}$ and $\omega^2_{Y|Z} = \omega^2_Y - \Omega_{XY}\Omega_Z^{-1}\Omega_{ZY}$ are the partial variances of X and Y, respectively After taking into account the impact that Z has on both X and Y, partial correlation measures the degree of association between X and Y. It indicates the degree to which X and Y are related to each other, regardless of their reciprocal relationship with Z (see Werme et al. (2022) for further details).

2.4 Functional enrichment of genes shared between LST and levels of inflammatory markers

We conducted analyses to investigate the functional enrichment of genes for which we identified a significant local genetic correlation between LST and levels of inflammatory markers. Functional enrichment analysis allows to identify trends in large scale biological datasets and is commnonly applied in to gain insights in disease and drug function mechanisms (Wijesooriya et al. 2022) . First, we investigated whether significant genes are enriched for Panther pathways and gene ontology (GO) terms using the over-representation analysis (ORA) method implemented in webGestalt (Liao et al. 2019), adjusting results based on false discovery rate (FDR). In Pathway and GO term analyses conducted with ORA, a list of genes of interest (in our case the list of genes showing a significant correlation between LST and inflammatory markers) is queried against a gene set to determine whether the number of genes belonging to a particular gene set is higher compared to that expected by chance (Wijesooriya et al. 2022). GO comprises three ontologies (i.e. vocabularies for representing domain knowledge): molecular function, biological process, and cellular component. In this system, the ontology is a tree-like hierarchical structure of concepts, called GO terms, and their relationships. Starting from a list of genes found to be associated with a phenotype, GO enrichment analysis methods allow to determine whether GO terms about specific biological processes, molecular functions, or cellular components are over- or under-represented within the gene set of interest (Tomczak et al. 2018).

We also tested whether protein encoded by these genes showed a significant protein-protein enrichment using STRING (Szklarczyk et al. 2019). Understanding physical and functional interactions between proteins is important since, if proteins

associated with a particular trait interact with each other, and are therefore involved in the same biological processes, this is a hint that those biological processes might play a relevant role in our trait of interest. A significant protein-protein interaction (PPI) score indicates that the identified proteins have more interactions among themselves than would be expected for a random set of proteins of the same size and degree distribution drawn from the genome. For these analyses, the interaction score was set to medium confidence as default and all interaction sources were included (text mining, experiments, databases, co-expression, neighborhood, gene fusion and co-occurrence). Finally, for all genes we extracted information from the Drug Gene Interaction Database (DGIdb) (Cotto et al. 2018) to assess whether the proteins they encode are 'potentially druggable' or clinically actionable based on their involvement in selected pathways, molecular functions or gene families (druggable genome), according to information retrieved from different drug target repositories (including DrugBank, PharmGKB, Chembl, Drug Target Commons and Therapeutic Target Database). Functional enrichment analyses require a list of genes, or proteins encoded by genes, and were therefore not conducted on results related to large genomic loci, since these loci contain several genes and results obtained with LAVA do not allow to distinguish which specific genes present in the locus might be involved.

3 Results

3.1 Global genetic correlation

Analyses conducted with LDSC showed that LST was significantly positively correlated with genetically predicted circulating levels of both CRP ($r_g = 0.37$, standard error = 0.03, p = 1.6E-34) and IL6 ($r_g = 0.41$, standard error = 0.07, p = 1.1E-08), supporting the hypothesis that, when considering the average of genetic signals across the genome, being predisposed to high sedentary time also predisposes to higher risk of systemic inflammation.

3.2 Local genetic correlation

Using local genetic correlation analyses based on the definition of genomic loci proposed in LAVA, we identified 80 loci for which a significant local heritability for both traits was suggested by results of the univariate test (i.e. a significant p-value adjusted for Bonferroni was obtained) and therefore for which bivariate correlation analyses were conducted (Table 9). Of these, 20 loci were significantly shared between LST and levels of CRP after multiple testing correction. Results for these loci are reported in Table 1. All loci showed a positive correlation (i.e. a locus associated with increased LST is also associated with increased levels of the inflammatory marker), potentially supporting the hypothesis that higher sedentary time as represented with LST is associated with higher levels of inflammation.

Using local genetic correlation analyses based on the gene-based definition of genomic loci proposed in this study, we identified 99 genes for which bivariate

Table 1 Genomic loci shared between LST and CRP levels

Locus	SNPs	ρ	ρ_L	ρ_U	p	p_{adj}
19:45040933-45893307	2460	0.80	0.64	1.00	1.3E-18	1.0E-16
3:47588462-50387742	3748	0.73	0.57	0.89	2.0E-13	1.6E-11
11:45019560-46316005	3318	0.82	0.61	1.00	9.0E-10	7.2E-08
4:139553761-141087047	4008	0.94	0.68	1.00	5.1E-09	4.1E-07
1:97721187-99425000	4607	0.84	0.59	1.00	1.1E-08	8.7E-07
6:43770627-44596897	2528	0.82	0.57	1.00	6.3E-08	5.1E-06
19:1515921-2253174	2323	0.64	0.43	0.86	1.1E-07	8.6E-06
20:62179242-62963627	2408	0.53	0.35	0.72	2.2E-07	1.8E-05
11:66782662-68000949	3052	0.83	0.57	1.00	3.0E-07	2.4E-05
3:71223282-72334704	3319	1.00	0.67	1.00	3.4E-07	2.7E-05
3:50387743-51953968	2545	0.66	0.44	0.88	3.6E-07	2.9E-05
11:64594823-66782661	3920	0.65	0.42	0.91	9.2E-07	7.4E-05
7:100849308-101950748	3750	0.83	0.51	1.00	2.1E-05	0.002
20:41351515-42185671	2349	0.71	0.41	1.00	4.3E-05	0.003
5:77290256-79005158	4440	0.63	0.35	0.93	4.9E-05	0.004
3:42301658-44141693	4602	0.70	0.37	1.00	1.0E-04	0.008
11:32830423-33905327	2835	0.61	0.33	0.94	1.2E-04	0.010
10:21477693-23365685	3937	0.65	0.35	0.99	1.4E-04	0.011
11:60515106-61717117	2590	0.59	0.31	0.94	2.3E-04	0.019
9:14244748-14902924	2402	0.42	0.20	0.66	0.001	0.047

The locus column indicates chromosome, start and stop of each locus in the hg19 build based on the LAVA genome partitioning algorithm; the SNPs column indicates the number of SNPs located in each gene in our datasets; the ρ, ρ_L and ρ_U columns indicate the linear correlation coefficient and the 95% confidence intervals; the p and p_{adj} columns report the p-value and adjusted p-value based on 80 bivariate genetic correlation tests

correlation analyses were conducted (Table 10). Loci corresponding to these genes were selected for the bivariate genetic correlation analysis based on the significant local heritability identified for both traits by univariate analyses. Of these, 59 genes were significantly shared between LST and levels of CRP after multiple testing correction. Results for these genes are reported in Table 2). Also in this case, for all these genes we observed a positive correlation between LST and genetically-determined CRP levels.

Genes significantly associated with LST and CRP levels are enriched for the glutamatergic synapse cellular component GO term (GO:0098978, $p = 0.0002$, FDR = 0.04, enrichment ratio = 5.4, genes: APOE, BSN, CAMKV, CNIH2, DAG1, RHOA and SEMA3F). In addition, analyses conducted with STRING showed that the proteins encoded by these genes have a significant PPI ($p = 2.0E\text{-}10$), suggesting that some of them are biologically connected since they have more interactions among themselves than what would be expected for a random set of proteins of the same size and degree distribution drawn from the genome. The networks of biologically related proteins encoded by these genes are shown in Fig. 1.

Analyses conducted based on information extracted from DGIdb showed that 20 of the identified genes are druggable or clinically actionable based on DGIdb:

Table 2 Genes shared between LST and CRP levels

Gene	Location	SNPs	ρ	ρ_L	ρ_U	p	p_{adj}
MON1A	3:49946301-49967445	26	0.93	0.81	1.00	1.2E-11	1.1E-09
SEMA3F-AS1	3:50153454-50193518	69	0.85	0.71	0.98	1.3E-11	1.3E-09
RNF123	3:49726949-49758962	51	0.93	0.79	1.00	1.4E-10	1.3E-08
CDHR4	3:49828166-49837254	17	0.95	0.84	1.00	3.2E-10	3.2E-08
IP6K1	3:49761727-49823973	100	0.83	0.67	0.98	4.3E-10	4.2E-08
TRAIP	3:49866027-49893992	39	0.94	0.81	1.00	8.3E-10	8.2E-08
MST1R	3:49924435-49941306	24	0.88	0.73	1.00	2.4E-09	2.3E-07
TOMM40	19:45394476-45406946	50	0.80	0.61	0.99	3.6E-09	3.5E-07
KCND3	1:112318453-112531777	703	0.80	0.58	1.00	7.9E-09	7.7E-07
UBA7	3:49842637-49851391	8	0.99	0.91	1.00	8.7E-09	8.6E-07
PRKAR2A	3:48788092-48885270	71	0.79	0.61	0.96	1.1E-08	1.1E-06
DAG1	3:49507564-49573051	108	0.86	0.68	1.00	1.2E-08	1.2E-06
CAMKV	3:49895421-49907369	15	0.90	0.76	1.00	1.6E-08	1.6E-06
RBM6	3:49977476-50114685	261	0.71	0.53	0.89	2.1E-08	2.0E-06
USP4	3:49314576-49377536	73	0.83	0.65	1.00	2.1E-08	2.1E-06
APOC1	19:45417920-45422606	11	0.82	0.63	1.00	2.8E-08	2.7E-06
RBM5	3:50126340-50156397	30	0.91	0.75	1.00	6.4E-08	6.2E-06
GNAI2	3:50273646-50296786	33	0.97	0.80	1.00	1.6E-07	1.5E-05
QRICH1	3:49067141-49131504	62	0.76	0.57	0.96	1.8E-07	1.8E-05
CACNA2D2	3:50400230-50540892	268	0.85	0.62	1.00	3.6E-07	3.5E-05
SEMA3F	3:50192847-50226508	66	0.73	0.53	0.92	4.2E-07	4.1E-05
BSN	3:49591921-49708982	150	0.70	0.50	0.90	6.6E-07	6.5E-05
PACS1	11:65837823-66012218	298	0.85	0.61	1.00	7.9E-07	7.8E-05
RHOA	3:49396578-49449526	90	0.89	0.69	1.00	8.6E-07	8.4E-05
SLC25A20	3:48894355-48936426	45	0.74	0.52	0.94	1.3E-06	1.3E-04
IGF2BP1	17:47074773-47133507	105	0.92	0.69	1.00	2.0E-06	1.9E-04
APOE	19:45409038-45412650	5	0.76	0.53	0.96	2.2E-06	2.2E-04
CNIH2	11:66045671-66051685	5	0.99	0.87	1.00	2.4E-06	2.3E-04
IL27	16:28510682-28518155	15	0.99	0.87	1.00	2.5E-06	2.5E-04
RAD54L2	3:51575595-51697612	98	0.89	0.65	1.00	2.8E-06	2.7E-04
IP6K2	3:48725435-48754920	48	0.80	0.57	1.00	3.3E-06	3.2E-04
ARIH2	3:48956280-49022971	66	0.68	0.47	0.89	3.3E-06	3.2E-04
DOCK3	3:50712671-51421629	1276	0.63	0.41	0.86	3.6E-06	3.5E-04
MAPKAPK3	3:50654561-50686728	50	0.86	0.65	1.00	4.7E-06	4.6E-04
CUX1	7:101460881-101901513	1102	0.77	0.48	1.00	6.4E-06	6.2E-04
COL7A1	3:48601505-48632593	31	0.84	0.60	1.00	8.3E-06	8.2E-04
RAB1B	11:66036055-66044963	18	1.00	0.82	1.00	1.1E-05	0.001
SLC38A3	3:50242691-50258406	23	0.83	0.60	1.00	1.4E-05	0.001
RP11-867G23.3	11:66037719-66045996	18	0.95	0.74	1.00	1.7E-05	0.002
C3orf84	3:49215068-49229291	18	0.77	0.53	0.98	2.9E-05	0.003
KLC2	11:66025173-66035332	13	1.00	0.84	1.00	3.3E-05	0.003
NICN1	3:49459765-49466757	9	0.83	0.60	1.00	4.9E-05	0.005

Table 2 (continued)

Gene	Location	SNPs	ρ	ρ_L	ρ_U	p	p_{adj}
GNAT1	3:50229042-50235129	4	1.00	0.89	1.00	5.0E-05	0.005
IHO1	3:49236932-49295537	85	0.66	0.40	0.90	5.4E-05	0.005
CATSPER1	11:65784222-65793988	23	0.93	0.71	1.00	5.8E-05	0.006
C3orf18	3:50595455-50608458	18	1.00	0.79	1.00	7.7E-05	0.008
DCAF1	3:51433297-51534018	138	0.70	0.41	0.98	8.8E-05	0.009
YIF1A	11:66052050-66056638	7	1.00	0.86	1.00	1.1E-04	0.011
TCTA	3:49449638-49453909	8	0.81	0.53	1.00	1.5E-04	0.014
RP11-949J7.8	3:49454210-49460111	7	0.81	0.53	1.00	1.7E-04	0.016
RBM15B	3:51428698-51435336	8	0.86	0.58	1.00	1.7E-04	0.017
P4HTM	3:49027340-49044581	16	0.68	0.40	0.93	2.1E-04	0.020
GAL3ST3	11:65808235-65816651	20	0.76	0.47	1.00	2.3E-04	0.022
BSN-DT	3:49586738-49591799	3	0.86	0.60	1.00	2.8E-04	0.027
MST1	3:49721379-49726196	9	0.88	0.60	1.00	3.6E-04	0.035
SF3B2	11:65819815-65836382	21	0.69	0.40	0.95	3.9E-04	0.038
RTN4RL1	17:1837970-1928178	337	0.59	0.30	0.90	4.6E-04	0.045
GNG12-AS1	1:68297970-68668670	1142	0.55	0.27	0.85	4.7E-04	0.046

Location indicates coordinates of each gene based on start and stop in the hg19 build according to UCSC; the SNPs column indicates the number of SNPs located in each gene in our datasets; the ρ, ρ_L and ρ_U columns indicate the linear correlation coefficient and the 95% confidence interval; the p and p_{adj} columns report the p-value and adjusted p-value according to the number of bivariate genetic correlation tests (n = 99)

MAPKAPK3, DAG1, RBM5, RNF123, IL27, SLC25A20, RHOA, APOC1, APOE, CUX1, P4HTM, COL7A1, CAMKV, RTN4RL1, CATSPER1, CACNA2D2, SEMA3F, MST1R, MST1 and KCND3.

Using local genetic correlation analyses based on the definition of genomic loci proposed in LAVA, we only identified 3 loci with a significant local heritability based on univariate analyses, all located in chromosome 6. For all three loci, we observed a significant positive correlation between LST and levels of IL6 after multiple testing correction (Table 3).

Using local genetic correlation analyses based on the gene-based definition of genomic loci proposed in this study, we identified 17 genes for which bivariate correlation analyses were conducted (Table 4) based on the significant local heritability identified by univariate analyses. Of these, 3 genes were significantly shared between LST and levels of IL6 after multiple testing correction (Table 4). Also in this case, all significant genes showed a positive correlation.

These three genes are part of the human leukocyte antigen (HLA) complex, a region located on the short arm of chromosome 6 that contains the most polymorphic gene cluster of the entire human genome and encodes proteins that play a crucial role in the function of the immune system. Accordingly, encoded proteins are enriched for the antigen binding molecular function GO term (p = 1.9E-05, FDR = 0.006,

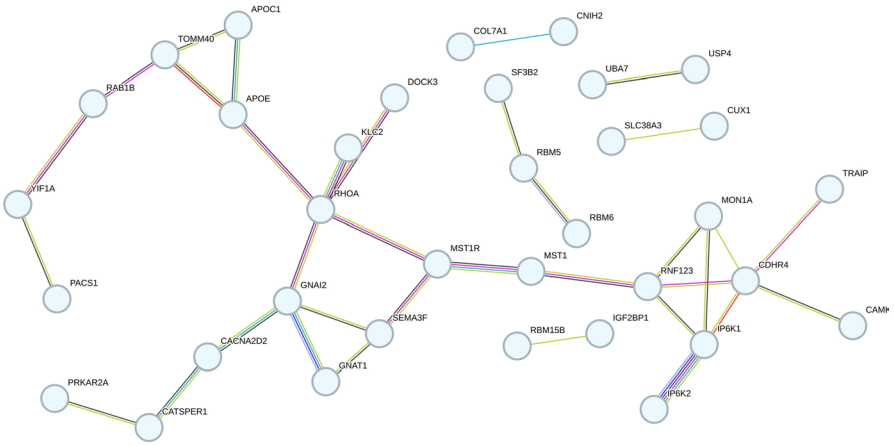

Fig. 1 Network of protein-protein interactions between genes shared between LST and CRP levels The figure shows the network of protein-protein interactions among proteins encoded by genes shared between LST and CRP levels. Nodes represent proteins while lines connecting nodes represent different types of sources of interactions (light blue: curated databases; pink: experimentally-determined; green: gene neighborhood; red: gene fusions; blue: gene co-occurrence; yellow: text-mining; black: co-expression; and violet: protein homology) (color figure online)

Table 3 Genomic loci shared between LST and IL6 levels

Locus	SNPs	ρ	ρ_L	ρ_U	p	p_{adj}
6:32454578-32539567	3036	0.85	0.67	1.00	9.3E-14	2.8E-13
6:32629240-32682213	2476	0.96	0.76	1.00	4.7E-13	1.4E-12
6:32539568-32586784	2153	0.48	0.31	0.66	6.4E-07	1.9E-06

The locus column indicates chromosome, start and stop of each locus in the hg19 build based on the LAVA genome partitioning algorithm; the SNPs column indicates the number of SNPs in each gene in our datasets; the ρ, ρ_L and ρ_U columns indicate the linear correlation coefficient and the 95% confidence intervals; the p and p_{adj} columns report the p-value and adjusted p-value based on the number of bivariate genetic correlation tests (n = 3)

enrichment ratio = 224.1, genes: HLA-DQA1 and HLA-DRB5) and the MHC protein complex cellular component GO term (p = 4.0E-06, FDR = 0.0007, enrichment ratio = 480.0, genes: HLA-DQA1 and HLA-DRB5). In addition, protein encoded by these genes show a significant PPI interaction score (p = 0.01) and all genes are part of the druggable genome or clinically actionable based on DGIdb. While these results should be interpreted cautiously, due to the fact that the HLA region is characterized by a strong LD (Werme et al. 2022), the involvement of the HLA system in the shared heritability between LST and IL6 levels is in line with previous studies suggesting that the lack of physical activity might be associated with alterations of immune function such as immunosenescence, a term that refers to the gradual deterioration of immune system generally observed with aging (Shao et al. 2021).

Table 4 Genes shared between LST and IL6 levels

Gene	Location	SNPs	ρ	ρ_L	ρ_U	p	p_{adj}
HLA-DRB5	6:32485153-32498006	442	0.64	0.51	0.77	1.5E-15	2.6E-14
HLA-DQA1	6:32605182-32611429	554	0.81	0.60	1.00	7.7E-10	1.3E-08
HLA-DRB6	6:32520489-32527779	343	0.62	0.42	0.82	1.6E-07	2.6E-06
IGSF21	1:18434239-18704977	1242	−0.46	−0.82	−0.16	0.003	0.053
RBM47	4:40425271-40631883	800	0.30	0.01	0.60	0.038	0.639
DGKG	3:185864989-186080023	681	0.29	0.00	0.60	0.046	0.789
EPHB2	1:23037330-23241823	706	0.05	−0.32	0.41	0.793	1.00
NTNG1	1:107682628-108024475	986	0.15	−0.15	0.44	0.312	1.00
KCNN3	1:154669941-154842754	616	−0.01	−0.23	0.22	0.963	1.00
ABLIM2	4:7967036-8160559	1005	0.18	−0.15	0.51	0.263	1.00
C5orf66	5:134368969-134680370	1027	0.19	−0.12	0.51	0.210	1.00
ARHGEF10	8:1772148-1906807	880	0.11	−0.27	0.48	0.541	1.00
GFRA1	10:117816441-118033126	815	0.09	−0.18	0.35	0.494	1.00
ABTB2	11:34172533-34379555	879	0.20	−0.14	0.55	0.245	1.00
SETBP1	18:42260862-42648475	1053	0.22	−0.03	0.48	0.083	1.00
CELSR1	22:46756730-46933067	1042	0.25	−0.03	0.54	0.090	1.00
MBP	18:74690788-74844774	870	0.25	−0.10	0.61	0.151	1.00

Location indicates coordinates of each gene based on start and stop in the hg19 build according to UCSC; the SNPs column indicates the number of SNPs located in each gene in our datasets; the ρ, ρ_L and ρ_U columns indicate the linear correlation coefficient and the 95% confidence interval; the p and p_{adj} columns report the p-value and adjusted p-value according to the number of bivariate genetic correlation tests (n = 17)

3.3 Comparison of results obtained with different genomic loci definitions

The analyses conducted using the standard or modified definition of genomic loci provided complementary results. As regards to genetic determinants shared between LST and CRP levels, we identified five loci (3:47588462-50387742, 3:50387743-51953968, 7:100849308-101950748, 11:64594823-66782661, and 19:45040933-45893307) for which a significant association was also identified when loci were defined based on gene coordinates. This observation suggests that, for these loci, the contribution of specific genes such as e.g. CUX1 for the 7:100849308-101950748 locus is relevant. Conversely, for the other loci identified as significant in the first analysis, we did not identify specific genes involved in the signals. This observation suggest that, for these loci, shared genetic signals are not restricted to specific genes but are more sparse across the locus, thus making it challenging to explore the functional enrichment of the observed results. Finally, we also identified significant genes that did not correspond to loci significant in the main analysis: KCND3 and GNG12-AS1 on chromosome 1, IL27 on chromosome 16, RTN4RL1 and IGF2BP1 on chromosome 17. In these cases, we can speculate that the shared genetic signal mainly involves these specific genes. In the case of LST and IL6 levels, results obtained using the two approaches allowed to obtain similar results. Specifically, all identified genes and loci were related to the HLA locus.

Table 5 Genomic loci shared between LST and CRP levels: partial correlation adjusted for BMI

Locus	ρ	ρ_L	ρ_U	p	p_{adj}
3:47588462-50387742	0.57	0.37	0.80	5.6E-07	1.6E-05
11:45019560-46316005	0.69	0.42	1.00	8.0E-06	0.0002
1:97721187-99425000	0.68	0.42	1.00	8.2E-06	0.0002
3:50387743-51953968	0.57	0.31	0.86	5.9E-05	0.001
11:32830423-33905327	0.54	0.26	0.88	5.0E-04	0.010
6:43770627-44596897	0.68	0.30	1.00	0.001	0.019
11:66782662-68000949	0.58	0.26	1.00	0.003	0.019
20:62179242-629636278	0.48	0.20	0.93	0.003	0.019
19:1515921-2253174	0.45	0.18	0.76	0.002	0.038
3:71223282-72334704	0.93	0.35	1.00	0.003	0.057
19:45040933-45893307	0.42	0.13	0.75	0.005	0.095
11:64594823-66782661	0.39	0.11	0.70	0.008	0.152
4:139553761-141087047	0.42	−0.52	1.00	0.25	1.00
20:41351515-42185671	0.43	−0.03	1.00	0.06	1.00
5:77290256-79005158	0.25	−0.48	0.85	0.36	1.00
3:42301658-44141693	0.04	−1.00	1.00	0.91	1.00
10:21477693-23365685	0.04	−1.00	1.00	0.92	1.00
11:60515106-61717117	0.22	−0.18	0.63	0.25	1.00
9:14244748-14902924	0.26	−0.05	0.61	0.10	1.00

The locus column indicates chromosome, start and stop of each locus in the hg19 build based on the LAVA genome partitioning algorithm; the ρ column indicates the partial correlation coefficient; the ρ_L and ρ_U columns indicate the 95% confidence interval; the p and p_{adj} columns report the p-value and adjusted p-value according to the number of partial correlation tests (n = 19)

3.4 Partial genetic correlation adjusted for BMI

Partial correlation between LST and CRP, adjusted for BMI, was conducted for 19 of the 20 loci significantly shared between the two phenotypes and showing a significant local heritability for all traits. For 10 out of the 19 loci we found that the association was no longer significant, suggesting that the association between LST and CRP levels is largely mediated by BMI (Table 5). However, we also identified nine loci for which the association was deemed to be independent from BMI, as the correlation coefficient was only slightly changed and they were still significant when adjusting for BMI.

Partial correlation between LST and CRP, adjusted for BMI, could be conducted for 48 genes. While for 29 genes we found that the association between LST and CRP levels was entirely mediated by BMI, for 19 genes the association was still significant after the adjustment (Table 6).

Partial correlation between LST and IL6 adjusting for BMI could be conducted for three loci (Table 7) and two genes (Table 8). In all cases, the genetic correlation between LST and IL6 levels was found to be independent from BMI.

4 Conclusions

In this study, we sought to identify shared genetic determinants between sedentary time, defined based on LST, and genetically-determined inflammatory markers (CRP and IL6) using local genetic correlation analysis, a statistical method that does not analyze the signals across the genome globally but allows the analysis of specific genomic loci. We compare results obtained with a standard definition of genomic loci, based on the genome partitioning algorithm implemented in LAVA, with a proposed modified version in which loci are defined based on gene coordinates. We show how this method allows to identify specific genes shared between two traits, rather than large genomic loci comprising multiple genes, thus enabling to conduct analyses focused on specific targets, such as evaluation of functional enrichment. We identified several loci shared between LST and inflammation and dissected those for which the association was mediated by or independent from BMI. This analysis was motivated by the fact that BMI is known to be associated with both sedentary behaviour and inflammation, and it is therefore plausible that it could mediate some of the observed associations between the two traits. While some of the associations we identified were mediated by BMI, we also identified associations independent from this trait, suggesting the existence of shared genetic determinants that predispose to spend more time in sedentary behaviours (in our study represented by LST) and to increased inflammation, through mechanisms independent from BMI. We can speculate that these mechanisms might also include increase susceptibility to infections, since we identified some of the shared genetic signals between LST and IL6 to be related to the HLA region, which encodes proteins crucial for immune function. This speculation is in line with results from a previous study showing that prepandemic physical activity has been previously shown to represent a protective factor associated with lower risk and severity of COVID-19 (Ma et al. 2023). However, since our study did not include any analysis on traits related to susceptibility to infections, furhter studies are needed to explore this aspect.

Sedentary behaviour represents a problem for the general population, having been identified by the World Health Organization as a significant risk factor for global mortality (Shao et al. 2021). However, even in people who are engaged in moderate- and vigorous-intensity physical activity, such as athletes, high levels of LST, for instance during recovery (Franssen et al. 2022), can compromise the body composition, regardless of weekly training time (Júdice et al. 2022). Unfortunately, the GWAS datasets we analyzed do not include information on the levels of physical activity of participants. Future studies able to stratify participants based on their levels of physical activity, as well as studies focused on athletes for which information on both levels of activity and LST during recovery time are available, are needed to verify whether the association between LST and inflammatory markers may vary based on different levels of physical activity.

Our results should be interpreted in light of some limitations. First, our study only investigated the genetic component of LST and levels of inflammatory markers. However, these traits represent complex phenotypes in which genetics interacts with environmental factors. Secondly, the GWAS datasets analyzed in this study only included participants of European origin, due to the under-representation of diverse population in GWAS studies. This might impact the generalizability of these findings to other populations. In addition,

Table 6 Genes shared between LST and CRP levels: partial correlation adjusted for BMI

Gene	Location	ρ	ρ_L	ρ_U	p	p_{adj}
MAPKAPK3	3:5065456150686728	0.93	0.75	1.00	1.1E-06	5.3E-05
CACNA2D2	3:5040023050540892	0.83	0.57	1.00	4.0E-06	1.9E-04
IL27	16:2851068228518155	0.92	0.67	1.00	5.1E-06	2.4E-04
KCND3	1:112318453112531777	0.88	0.56	1.00	7.2E-06	3.5E-04
RBM15B	3:5142869851435336	0.98	0.81	1.00	3.2E-05	0.002
GNAI2	3:5027364650296786	0.95	0.72	1.00	3.4E-05	0.002
RAB1B	11:6603605566044963	1.00	0.80	1.00	8.0E-05	0.004
C3orf18	3:5059545550608458	1.00	0.82	1.00	9.9E-05	0.005
IP6K1	3:4976172749823973	0.73	0.46	1.00	1.0E-04	0.005
MON1A	3:4994630149967445	0.82	0.56	1.00	1.0E-04	0.005
RP11-867G23.3	11:6603771966045996	1.00	0.81	1.00	1.0E-04	0.005
CNIH2	11:6604567166051685	1.00	0.89	1.00	0.0003	0.014
RNF123	3:4972694949758962	0.83	0.51	1.00	4.0E-04	0.019
KLC2	11:6602517366035332	1.00	0.83	1.00	0.0004	0.019
CDHR4	3:4982816649837254	0.88	0.59	1.00	7.0E-04	0.034
QRICH1	3:4906714149131504	0.65	0.34	0.99	0.0007	0.034
BSN	3:4959192149708982	0.62	0.32	0.98	0.0007	0.034
ARIH2	3:4895628049022971	0.60	0.30	0.91	0.0007	0.034
SEMA3F-AS1	3:5015345450193518	0.64	0.32	0.98	0.001	0.048
PRKAR2A	3:4878809248885270	0.59	0.26	0.94	0.002	0.096
SEMA3F	3:5019284750226508	0.56	0.25	0.88	0.002	0.096
IP6K2	3:4872543548754920	0.50	0.21	0.80	0.002	0.096
DOCK3	3:5071267151421629	0.50	0.21	0.81	0.002	0.096
DCAF1	3:5143329751534018	0.61	0.29	0.97	0.002	0.096
GNG12-AS1	1:6829797068668670	0.54	0.22	0.99	0.002	0.096
RHOA	3:4939657849449526	0.73	0.34	1.00	0.003	0.144
SLC25A20	3:4889435548936426	0.60	0.27	0.92	0.003	0.144
YIF1A	11:6605205066056638	1.00	0.86	1.00	0.003	0.144
DAG1	3:4950756449573051	0.70	0.30	1.00	0.004	0.192
RBM6	3:4997747650114685	0.53	0.20	0.86	0.004	0.192
RAD54L2	3:5157559551697612	0.71	0.31	1.00	0.004	0.192
SLC38A3	3:5024269150258406	0.73	0.32	1.00	0.005	0.240
PACS1	11:6583782366012218	0.63	0.23	1.00	0.007	0.336
IHO1	3:4923693249295537	0.77	0.21	1.00	0.020	0.960
P4HTM	3:4902734049044581	0.58	0.14	1.00	0.020	0.96
MST1R	3:4992443549941306	0.69	0.16	1.00	0.030	1.00
TOMM40	19:4539447645406946	0.27	−0.84	1.00	0.490	1.00
UBA7	3:4984263749851391	1.00	0.56	1.00	0.040	1.00
CAMKV	3:4989542149907369	0.47	−0.45	1.00	0.190	1.00
USP4	3:4931457649377536	0.81	0.05	1.00	0.070	1.00
APOC1	19:4541792045422606	0.79	0.04	1.00	0.080	1.00
RBM5	3:5012634050156397	0.60	−0.05	1.00	0.070	1.00

Table 6 (continued)

Gene	Location	ρ	ρ_L	ρ_U	p	p_{adj}
C3orf84	3:4921506849229291	0.45	−0.32	1.00	0.150	1.00
CATSPER1	11:6578422265793988	1.00	−1.00	1.00	0.240	1.00
GAL3ST3	11:6580823565816651	0.56	−0.08	1.00	0.070	1.00
MST1	3:4972137949726196	0.52	−0.62	1.00	0.250	1.00
SF3B2	11:6581981565836382	0.54	0.01	0.98	0.040	1.00
RTN4RL1	17:18379701928178	0.45	0.07	0.87	0.030	1.00

Location indicates coordinates of each gene based on start and stop in the hg19 build according to UCSC; the ρ column indicates the partial correlation coefficient the ρ_L and ρ_U columns indicate the 95% confidence interval; the p and p_{adj} columns report the p-value and adjusted p-value according to the number of partial correlation tests (n = 48)

Table 7 Genomic loci shared between LST and IL6 levels: partial correlation adjusted for BMI

Locus	ρ	ρ_L	ρ_U	p	p_{adj}
6:32454578-32539567	0.89	0.79	0.99	6.2E-25	1.9E-24
6:32629240-32682213	0.83	0.71	0.95	3.6E-20	1.1E-19
6:32539568-32586784	0.61	0.36	0.59	3.9E-05	1.2E-04

The locus column indicates chromosome, start and stop of each locus in the hg19 build based on the LAVA genome partitioning algorithm; the ρ column indicates the partial correlation coefficient; the ρ_L and ρ_U columns indicate the 95% confidence interval; the p and p_{adj} columns report the p-value and adjusted p-value according to the number of partial correlation tests (n = 19)

Table 8 Genes shared between LST and IL6 levels: partial correlation adjusted for BMI

Gene	Location	ρ	ρ_L	ρ_U	p	p_{adj}
HLA-DRB6	6:32520489-32527779	0.93	0.78	1.00	6.7E-08	1.3E-07
HLA-DQA1	6:32605182-32611429	0.54	0.36	0.73	9.2E-07	1.8E-06

Location indicates coordinates of each gene based on start and stop in the hg19 build according to UCSC; the ρ column indicates the partial correlation coefficient; the ρ_L and ρ_U columns indicate the 95% confidence interval; the p and p_{adj} columns report the p-value and adjusted p-value according to the number of partial correlation tests (n = 2)

since LST was the only measure of sedentary time investigated in this study, we cannot draw conclusions on other markers of sedentary time. To conclude, our study provides novel knowledge elucidating shared genetic determinants between sedentary behaviour and inflammation and suggest that the analysis of local genetic correlation conducted using both large genomic loci as well as loci defined based on gene coordinates can provide complementary information to identify pleiotropic genes.

Appendix A

See Tables 9 and 10.

Table 9 Genomic loci shared between LST and CRP levels

Locus	SNPs	ρ	ρ_L	ρ_U	p	p_{adj}
19:45040933-45893307	2460	0.80	0.64	1.00	1.3E-18	1.0E-16
3:47588462-50387742	3748	0.73	0.57	0.89	2.0E-13	1.6E-11
11:45019560-46316005	3318	0.82	0.61	1.00	9.0E-10	7.2E-08
4:139553761-141087047	4008	0.94	0.68	1.00	5.1E-09	4.1E-07
1:97721187-99425000	4607	0.84	0.59	1.00	1.1E-08	8.7E-07
6:43770627-44596897	2528	0.82	0.57	1.00	6.3E-08	5.1E-06
19:1515921-2253174	2323	0.64	0.43	0.86	1.1E-07	8.6E-06
20:62179242-62963627	2408	0.53	0.35	0.72	2.2E-07	1.8E-05
11:66782662-68000949	3052	0.83	0.57	1.00	3.0E-07	2.4E-05
3:71223282-72334704	3319	1.00	0.67	1.00	3.4E-07	2.7E-05
3:50387743-51953968	2545	0.66	0.44	0.88	3.6E-07	2.9E-05
11:64594823-66782661	3920	0.65	0.42	0.91	9.2E-07	7.4E-05
7:100849308-101950748	3750	0.83	0.51	1.00	2.1E-05	0.002
20:41351515-42185671	2349	0.71	0.41	1.00	4.3E-05	0.003
5:77290256-79005158	4440	0.63	0.35	0.93	4.9E-05	0.004
3:42301658-44141693	4602	0.70	0.37	1.00	1.0E-04	0.008
11:32830423-33905327	2835	0.61	0.33	0.94	1.2E-04	0.010
10:21477693-23365685	3937	0.65	0.35	0.99	1.4E-04	0.011
11:60515106-61717117	2590	0.59	0.31	0.94	2.3E-04	0.019
9:14244748-14902924	2402	0.42	0.20	0.66	0.001	0.047
17:1480057-2699135	3496	0.45	0.20	0.71	0.001	0.081
7:71215742-73128830	3807	0.34	0.11	0.56	0.004	0.321
6:127545460-128763380	2622	0.46	0.15	0.78	0.004	0.343
10:65400432-66510387	2665	0.50	0.18	0.86	0.005	0.376
4:17290237-18753263	4608	0.48	0.16	0.82	0.005	0.378
1:153410810-154685545	2401	−0.23	−0.40	−0.07	0.005	0.426
14:77425454-78374053	3463	0.44	0.14	0.77	0.006	0.460
17:815654-1480056	2802	0.45	0.14	0.78	0.006	0.495
9:91643256-92500277	2552	0.38	0.12	0.67	0.006	0.505
17:7264459-8554763	3463	0.45	0.13	0.81	0.008	0.615
2:44104111-45189468	3211	0.46	0.15	0.82	0.008	0.631
16:72089512-73140781	2374	0.42	0.11	0.75	0.010	0.772
1:197935822-199263389	3660	0.38	0.10	0.69	0.010	0.794
5:58721459-59868567	2677	0.39	0.10	0.70	0.010	0.814
1:213958293-214783872	2477	0.40	0.10	0.71	0.011	0.889
4:23858351-24764724	2580	0.46	0.10	0.86	0.014	1.00
5:91956906-93814604	3110	0.33	0.05	0.61	0.019	1.00
18:12735559-13641479	2661	−0.32	−0.65	−0.06	0.020	1.00
2:169224446-170155561	2809	0.27	0.04	0.50	0.023	1.00
20:60766558-61470768	2334	0.39	0.05	0.75	0.027	1.00
1:34371023-35201626	2727	0.41	0.04	0.80	0.031	1.00
12:61737954-63055936	3840	0.39	0.03	0.76	0.033	1.00

Table 9 (continued)

Locus	SNPs	ρ	ρ_L	ρ_U	p	p_{adj}
6:16566883-17391994	2318	0.38	0.03	0.76	0.040	1.00
19:13213187-13968319	2222	0.29	−0.01	0.58	0.057	1.00
2:26894103-28819510	4072	0.17	−0.01	0.35	0.067	1.00
17:60453121-62112373	2802	0.29	−0.05	0.63	0.088	1.00
9:126092932-127184582	3041	0.22	−0.09	0.53	0.158	1.00
2:24669225-25895394	2755	0.21	−0.10	0.51	0.162	1.00
11:12470450-13364727	2670	0.16	−0.08	0.39	0.169	1.00
8:125453323-126766827	3868	0.17	−0.08	0.42	0.180	1.00
5:90793805-91956905	2484	0.23	−0.12	0.56	0.185	1.00
19:45893308-46765060	2569	0.16	−0.08	0.39	0.185	1.00
1:154685546-156813845	3756	0.15	−0.08	0.38	0.186	1.00
1:57529671-58387483	2739	0.24	−0.13	0.61	0.195	1.00
1:149716038-151146407	2728	-0.23	−0.68	0.13	0.216	1.00
7:40261241-41415925	2499	0.20	−0.13	0.53	0.217	1.00
1:66778016-67761890	2902	0.14	−0.09	0.36	0.222	1.00
8:143611462-144934288	4456	−0.17	−0.53	0.13	0.254	1.00
9:138995792-140097759	2478	0.17	−0.15	0.47	0.270	1.00
5:52139774-52837225	2505	0.19	−0.18	0.55	0.287	1.00
18:53762997-54957867	3219	−0.17	−0.56	0.15	0.301	1.00
3:4109394-4835083	2499	0.15	−0.19	0.46	0.357	1.00
17:42348004-43460500	2595	−0.13	−0.51	0.19	0.425	1.00
12:12721875-13559527	2337	0.12	−0.20	0.44	0.434	1.00
11:10370101-11081299	2377	0.12	−0.22	0.44	0.476	1.00
1:110224231-111134062	2509	0.13	−0.28	0.51	0.506	1.00
12:23923799-25058714	3701	−0.06	−0.29	0.15	0.569	1.00
12:21572253-22928055	3264	0.10	−0.29	0.46	0.593	1.00
5:51203266-52139773	3082	−0.07	−0.39	0.22	0.622	1.00
14:68976913-69794542	2561	−0.08	−0.50	0.27	0.642	1.00
5:63214090-64438518	2896	0.07	−0.34	0.44	0.698	1.00
12:11742150-12721874	3033	0.06	−0.33	0.43	0.728	1.00
9:66673059-70939677	1380	0.05	−0.31	0.37	0.768	1.00
12:63055937-63764111	2446	0.04	−0.41	0.43	0.829	1.00
12:99244338-100931423	4102	0.03	−0.34	0.37	0.845	1.00
14:23985937-24906056	2446	−0.03	−0.37	0.28	0.850	1.00
12:54371449-55416802	2765	−0.03	−0.37	0.28	0.870	1.00
12:48960266-50344346	2970	−0.01	−0.46	0.37	0.963	1.00
8:72917490-73838027	3043	0.00	−0.35	0.33	0.982	1.00

The locus column indicates chromosome, start and stop of each locus in the hg19 build based on the LAVA genome partitioning algorithm; the SNPs column indicates the number of SNPs located in each gene in our datasets; the ρ, ρ_L and ρ_U columns indicate the linear correlation coefficient and the 95% confidence intervals; the p and p_{adj} columns report the p-value and adjusted p-value according to the number of bivariate genetic correlation tests (n = 80)

Table 10 Genes shared between LST and CRP levels

Gene	Location	SNPs	ρ	ρ_L	ρ_U	p	p_{adj}
MON1A	3:49946301-49967445	26	0.93	0.81	1.00	1.2E-11	1.1E-09
SEMA3F-AS1	3:50153454-50193518	69	0.85	0.71	0.98	1.3E-11	1.3E-09
RNF123	3:49726949-49758962	51	0.93	0.79	1.00	1.4E-10	1.3E-08
CDHR4	3:49828166-49837254	17	0.95	0.84	1.00	3.2E-10	3.2E-08
IP6K1	3:49761727-49823973	100	0.83	0.67	0.98	4.3E-10	4.2E-08
TRAIP	3:49866027-49893992	39	0.94	0.81	1.00	8.3E-10	8.2E-08
MST1R	3:49924435-49941306	24	0.88	0.73	1.00	2.4E-09	2.3E-07
TOMM40	19:45394476-45406946	50	0.80	0.61	0.99	3.6E-09	3.5E-07
KCND3	1:112318453-112531777	703	0.80	0.58	1.00	7.9E-09	7.7E-07
UBA7	3:49842637-49851391	8	0.99	0.91	1.00	8.7E-09	8.6E-07
PRKAR2A	3:48788092-48885270	71	0.79	0.61	0.96	1.1E-08	1.1E-06
DAG1	3:49507564-49573051	108	0.86	0.68	1.00	1.2E-08	1.2E-06
CAMKV	3:49895421-49907369	15	0.90	0.76	1.00	1.6E-08	1.6E-06
RBM6	3:49977476-50114685	261	0.71	0.53	0.89	2.1E-08	2.0E-06
USP4	3:49314576-49377536	73	0.83	0.65	1.00	2.1E-08	2.1E-06
APOC1	19:45417920-45422606	11	0.82	0.63	1.00	2.8E-08	2.7E-06
RBM5	3:50126340-50156397	30	0.91	0.75	1.00	6.4E-08	6.2E-06
GNAI2	3:50273646-50296786	33	0.97	0.80	1.00	1.6E-07	1.5E-05
QRICH1	3:49067141-49131504	62	0.76	0.57	0.96	1.8E-07	1.8E-05
CACNA2D2	3:50400230-50540892	268	0.85	0.62	1.00	3.6E-07	3.5E-05
SEMA3F	3:50192847-50226508	66	0.73	0.53	0.92	4.2E-07	4.1E-05
BSN	3:49591921-49708982	150	0.70	0.50	0.90	6.6E-07	6.5E-05
PACS1	11:65837823-66012218	298	0.85	0.61	1.00	7.9E-07	7.8E-05
RHOA	3:49396578-49449526	90	0.89	0.69	1.00	8.6E-07	8.4E-05
SLC25A20	3:48894355-48936426	45	0.74	0.52	0.94	1.3E-06	1.3E-04
IGF2BP1	17:47074773-47133507	105	0.92	0.69	1.00	2.0E-06	1.9E-04
APOE	19:45409038-45412650	5	0.76	0.53	0.96	2.2E-06	2.2E-04
CNIH2	11:66045671-66051685	5	0.99	0.87	1.00	2.4E-06	2.3E-04
IL27	16:28510682-28518155	15	0.99	0.87	1.00	2.5E-06	2.5E-04
RAD54L2	3:51575595-51697612	98	0.89	0.65	1.00	2.8E-06	2.7E-04
IP6K2	3:48725435-48754920	48	0.80	0.57	1.00	3.3E-06	3.2E-04
ARIH2	3:48956280-49022971	66	0.68	0.47	0.89	3.3E-06	3.2E-04
DOCK3	3:50712671-51421629	1276	0.63	0.41	0.86	3.6E-06	3.5E-04
MAPKAPK3	3:50654561-50686728	50	0.86	0.65	1.00	4.7E-06	4.6E-04
CUX1	7:101460881-101901513	1102	0.77	0.48	1.00	6.4E-06	6.2E-04
COL7A1	3:48601505-48632593	31	0.84	0.60	1.00	8.3E-06	8.2E-04
RAB1B	11:66036055-66044963	18	1.00	0.82	1.00	1.1E-05	0.001
SLC38A3	3:50242691-50258406	23	0.83	0.60	1.00	1.4E-05	0.001
RP11-867G23.3	11:66037719-66045996	18	0.95	0.74	1.00	1.7E-05	0.002
C3orf84	3:49215068-49229291	18	0.77	0.53	0.98	2.9E-05	0.003
KLC2	11:66025173-66035332	13	1.00	0.84	1.00	3.3E-05	0.003
NICN1	3:49459765-49466757	9	0.83	0.60	1.00	4.9E-05	0.005

Table 10 (continued)

Gene	Location	SNPs	ρ	ρ_L	ρ_U	p	p_{adj}
GNAT1	3:50229042-50235129	4	1.00	0.89	1.00	5.0E-05	0.005
IHO1	3:49236932-49295537	85	0.66	0.40	0.90	5.4E-05	0.005
CATSPER1	11:65784222-65793988	23	0.93	0.71	1.00	5.8E-05	0.006
C3orf18	3:50595455-50608458	18	1.00	0.79	1.00	7.7E-05	0.008
DCAF1	3:51433297-51534018	138	0.70	0.41	0.98	8.8E-05	0.009
YIF1A	11:66052050-66056638	7	1.00	0.86	1.00	1.1E-04	0.011
TCTA	3:49449638-49453909	8	0.81	0.53	1.00	1.5E-04	0.014
RP11-949J7.8	3:49454210-49460111	7	0.81	0.53	1.00	1.7E-04	0.016
RBM15B	3:51428698-51435336	8	0.86	0.58	1.00	1.7E-04	0.017
P4HTM	3:49027340-49044581	16	0.68	0.40	0.93	2.1E-04	0.020
GAL3ST3	11:65808235-65816651	20	0.76	0.47	1.00	2.3E-04	0.022
BSN-DT	3:49586738-49591799	3	0.86	0.60	1.00	2.8E-04	0.027
MST1	3:49721379-49726196	9	0.88	0.60	1.00	3.6E-04	0.035
SF3B2	11:65819815-65836382	21	0.69	0.40	0.95	3.9E-04	0.038
RTN4RL1	17:1837970-1928178	337	0.59	0.30	0.90	4.6E-04	0.045
GNG12-AS1	1:68297970-68668670	1142	0.55	0.27	0.85	4.7E-04	0.046
APEH	3:49711434-49720934	7	0.85	0.56	1.00	7.3E-04	0.072
AX746604	11:65801869-65803659	7	0.82	0.52	1.00	8.4E-04	0.083
TEX264	3:51705289-51738339	36	0.61	0.29	0.90	0.001	0.145
CELSR3	3:48662830-48709981	52	0.65	0.31	0.97	0.002	0.165
SOX5	12:23685230-24102637	1104	0.42	0.16	0.68	0.003	0.283
FTO	16:53737874-54148379	1244	0.35	0.12	0.58	0.005	0.449
THRB	3:24158644-24536313	1161	0.39	0.11	0.67	0.008	0.812
ATXN1	6:16299342-16761721	1478	−0.43	−0.83	−0.12	0.009	0.836
KLC3	19:45843997-45854778	33	0.52	0.16	0.87	0.011	1.00
SLC39A1	1:153931574-153940660	13	−0.50	−0.87	−0.13	0.011	1.00
USP19	3:49146105-49158371	10	0.55	0.16	0.90	0.012	1.00
ST3GAL3	1:44173203-44396837	523	0.40	0.10	0.70	0.012	1.00
SULF2	20:46286149-46414808	508	0.34	0.07	0.61	0.017	1.00
PTPRF	1:43996546-44089343	254	0.43	0.10	0.76	0.017	1.00
CERS6	2:169312758-169631644	1003	0.43	0.09	0.79	0.017	1.00
KDM4A	1:44115796-44171189	95	0.39	0.07	0.70	0.023	1.00
TUBGCP4	15:43663312-43698240	55	0.37	0.03	0.70	0.037	1.00
CLRN1-AS1	3:150570270-150797617	571	0.34	0.01	0.67	0.045	1.00
AKT3	1:243663020-244006584	477	0.30	0.00	0.58	0.049	1.00
BUD23	7:73097897-73112551	45	0.34	−0.13	0.77	0.143	1.00
CILP2	19:19649073-19657468	18	0.34	−0.17	0.79	0.168	1.00
ZNF345	19:37341777-37370477	69	0.26	−0.18	0.66	0.228	1.00
USP3	15:63796709-63886839	204	0.23	−0.20	0.64	0.263	1.00
VTI1A	10:114206755-114578504	764	0.17	−0.17	0.48	0.307	1.00
MAML3	4:140637545-141075233	1091	0.13	−0.13	0.38	0.321	1.00
ARL15	5:53180613-53606403	1431	0.16	−0.18	0.49	0.335	1.00

Table 10 (continued)

Gene	Location	SNPs	ρ	ρ_L	ρ_U	p	p_{adj}
NCAN	19:19322781-19363061	94	−0.17	−0.59	0.19	0.353	1.00
NUP210L	1:153965167-154127592	226	−0.12	−0.40	0.14	0.356	1.00
RGS6	14:72399155-73033238	2307	0.10	−0.13	0.33	0.366	1.00
BABAM2	2:28113481-28561767	1074	0.10	−0.12	0.32	0.384	1.00
FARP1	13:98795433-99102023	1148	0.12	−0.23	0.44	0.465	1.00
TAFA2	12:62102028-62586620	1483	0.12	−0.24	0.46	0.471	1.00
GATAD2A	19:19496641-19619741	233	−0.13	−0.54	0.23	0.492	1.00
OPCML	11:132284874-132813037	1969	0.12	−0.25	0.47	0.492	1.00
ARHGEF3	3:56761445-57113336	1076	0.09	−0.27	0.43	0.582	1.00
FAM155A	13:107820878-108519460	2467	−0.09	−0.49	0.24	0.590	1.00
TM6SF2	19:19375173-19384074	28	−0.10	−0.50	0.30	0.617	1.00
PBX1	1:164528596-164821060	764	0.04	−0.29	0.35	0.800	1.00
ZFYVE1	14:73436158-73493920	236	−0.03	−0.32	0.25	0.855	1.00
ITPR1	3:4535031-4889524	1203	0.00	−0.23	0.22	0.991	1.00

Location indicates coordinates of each gene based on start and stop in the hg19 build according to UCSC; the SNPs column indicates the number of SNPs located in each gene in our datasets; the ρ, ρ_L and ρ_U columns indicate the linear correlation coefficient and the 95% confidence interval; the p and p_{adj} columns report the p-value and adjusted p-value according to the number of bivariate genetic correlation tests (n = 99)

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Data availibility GWAS datasets used in this study are publicly available. Gene coordinates based on UCSC are available at the OSF repository: https://osf.io/pkxwm.

Declarations

Conflict of interest None.

Ethical approval Ethics approval was obtained by the original GWAS studies.

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