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PII: S0889-1591(26)00827-5
DOI: https://doi.org/10.1016/j.bbi.2026.107079
Reference: YBRBI 107079

To appear in: *Brain, Behavior, and Immunity*

Received Date: 3 July 2026
Revised Date: 25 September 2026
Accepted Date: 17 October 2026

Please cite this article as: Otero, J., Urbarova, I., Wilsgaard, T., Colineaux, H., Nøst, T.H., Castagné, R., Nielsen, C.S., Neufcourt, L., Grimsgaard, S., Vuckovic, D., Chadeau-Hyam, M., Delpierre, C., Kelly-Irving, M., Sandanger, T.M., Farbu, E.H., Educational attainment and systemic inflammation: Evidence of a stable gradient from two measurements in the Tromsø study (2007–2016), *Brain, Behavior, and Immunity* (2026), doi: https://doi.org/10.1016/j.bbi.2026.107079

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Title

Educational attainment and systemic inflammation: evidence of a stable gradient from two measurements in the Tromsø Study (2007-2016)

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Abstract

Disadvantaged socioeconomic position (SEP) is associated with increased systemic inflammation. However, the mechanisms and potential persistence of these molecular differences remain poorly understood. We investigated the association between educational attainment, an indicator of SEP, and the levels of 52 plasma inflammatory proteins measured in the same individuals seven to eight years apart. We analyzed data from 909 participants of the sixth (2007–2008) and seventh (2015–2016) waves of the Tromsø Study, a longitudinal population-based study in Tromsø, Norway. Inflammatory protein levels were measured using the Olink Target 96 Inflammation panel and educational attainment was retrieved from questionnaires. Cross-sectional and longitudinal associations between educational attainment and inflammatory protein levels were assessed using multivariable linear models and linear mixed models, respectively. We identified a consistent association between higher educational attainment and lower levels of CCL20, CDCP1, and HGF, and higher levels of CST5 at both waves (FDR<0.1). In addition, we observed that higher educational attainment was associated with lower levels of CCL19, IL-6, and OSM, and higher levels of FGF19 at the second wave only. Nonetheless, all associations were attenuated after adjustment for lifestyle factors, body-mass index, health conditions, and medication. Longitudinal analyses indicated a stable educational gradient across the two waves, with no significant changes in the association between educational attainment and inflammatory protein levels. Our findings indicate a stable educational gradient in the levels of several plasma proteins involved in cell migration, growth, and tissue remodeling in adults, across the seven-to-eight-year period, with modifiable lifestyle factors and body-mass index substantially attenuating the education-protein associations.

Keywords

Educational attainment, Social Psychoneuroimmunology, Systemic inflammation, Inflammatory proteins, Longitudinal study, Tromsø Study, Health inequality.

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1. Introduction

Socioeconomic position (SEP) is an established determinant of health, influencing exposures, living conditions, and overall opportunities throughout the life course. The accumulated effect of these situated differences gives rise to a socioeconomic gradient, in which individuals with less advantaged SEP experience worse health outcomes such as higher risk of developing type 2 diabetes, cancer, and cardiovascular diseases compared to their more advantaged counterparts (Mackenbach et al., 2008; Van Kippersluis et al., 2010; Wagg et al., 2021). Increasing evidence suggests that systemic inflammation may be one of the key biological mechanisms through which SEP is embodied.

Social Psychoneuroimmunology is a recently coined term denoting an emerging field of research that examines how social factors relate to immune function (Muscatell, 2021). Previous studies have consistently associated disadvantaged SEP with higher circulating levels of systemic inflammation markers, such as interleukin 6 (IL-6) and C-reactive protein (CRP) (Berger et al., 2019; Muscatell et al., 2020). These markers are established risk factors for depression, cancer, atherosclerosis, and cardiovascular disease (Akbari & Hassan-Zadeh, 2018; Gémes et al., 2008; Ting et al., 2020; Zhu et al., 2022) mortality. More recently, studies using multiplex immunoassay panels have identified a socioeconomic gradient across broader panels of inflammatory proteins, including cytokines (e.g. colony-stimulating factors (CSF3), C-C motif chemokines (CCL11)), growth factors (e.g. Hepatocyte Growth Factor (HGF)), and tumor necrosis factor superfamily members (e.g. TNFSF14), as well as their potential mediating role between SEP and cardiovascular diseases (Castagné et al., 2016; Lin et al., 2025; Shafi et al., 2022). These broader panels allow for a more comprehensive characterization of cell functions and inflammatory pathways linked to social disadvantage beyond acute-phase markers.

Individual SEP is measured through indicators such as educational attainment, occupation, and income, which capture related but distinct dimensions. Among these, educational attainment is regarded as a highly comprehensive indicator, as it is typically completed in early adulthood and seldom changes thereafter, is strongly related to employment and income, and is less susceptible to be influenced by health status (reverse causality) compared to other indicators (Galobardes et al., 2006). Furthermore, higher educational attainment is strongly associated with health literacy and consequently healthier lifestyle habits such as not smoking and high leisure-time physical activity, as well as lower body-mass index (BMI), all of which are associated with lower levels of pro-inflammatory proteins in blood (Gleeson et al., 2011; Lawrence, 2017; Muscatell et al., 2020) .

Nonetheless, the association between SEP indicators and inflammatory proteins is often assessed using measurements at a single time point, which hinders the possibility of differentiating between short- and long-term inflammation or determining whether the association between SEP and systemic inflammation changes over time. Life course frameworks suggest that disadvantaged SEP can have a cumulative effect over the years (Neufcourt et al., 2024; Whitley et al., 2024). In studies with protein measurements at two time points, significant increases in IL-6 and CRP levels, associated with lower educational attainment and self-perceived socioeconomic position, have been reported in the US (Deverts et al., 2012; Jones et al., 2023). Meanwhile, one similar study reported that educational attainment and income were associated

with increase in CRP levels in the UK but not in Indonesia (Maharani, 2019). Moreover, less is known about the stability of the association between SEP and other inflammatory proteins, particularly in highly egalitarian settings where structural inequalities may be buffered by a comprehensive welfare system.

In this study, we investigated the association between educational attainment and the levels of 52 plasma inflammatory proteins for 909 individuals using repeated protein measurements at two time points, seven to eight years apart. First, we analyzed the association between educational attainment and protein levels at each time point cross-sectionally, aiming to identify proteins consistently associated with educational attainment at both time points. Second, we investigated the longitudinal changes of these associations, to identify whether the educational gradient in the inflammatory protein levels was changing across time points.

2. Materials and Methods

2.1. Study Sample

The Tromsø Study is a longitudinal population-based study conducted in Tromsø, Norway. Starting in 1974, the study spans over 50 years and includes 45,473 participants in at least one of seven completed waves. The general design has been similar among waves and includes questionnaires, biological samples, and physical examinations further described elsewhere(Jacobsen et al., 2012). For this study, we considered individuals who had participated in the sixth wave (Tromsø6), conducted between 2007 and 2008 (n = 12,984; 65.7% attendance) and the seventh wave (Tromsø7), conducted between 2015 and 2016 (n = 21,083; 64.7% attendance) (Eggen et al., 2013; Hopstock et al., 2022)

A subsample of Tromsø7's participants attended a second visit for further examination (n = 8,346). Of these, a random sample (n = 1,144) had available measurements of 92 inflammatory protein levels, measured from plasma samples drawn at Tromsø7 and analyzed in 2019. Within this group, we identified individuals who had also participated in Tromsø6 (n = 806) and measured their protein levels from frozen plasma samples drawn at Tromsø6 in a second batch in 2023. To increase the longitudinal sample size, we further added a random sample of individuals who participated in both waves (n = 149) and measured the protein levels from the respective plasma samples from each wave in the batch of 2023. In sum, inflammatory protein levels were measured for 1,293 individuals of which 955 had attended both Tromsø6 and Tromsø7 and had protein levels measured at both waves. (Fig. 1 and Supplementary Fig. S1).

All participants of the Tromsø Study provided informed consent prior to their participation. The Tromsø Study complies with the 1964 Declaration of Helsinki and has received approval from the Regional Committee for Medical and Health Research Ethics (REK) in Northern Norway (Ref. 2009/2536 for Tromsø6, and Ref. 2014/940 for Tromsø7). In addition, REK approval was granted for this research project (Ref. 817197).

2.2. Educational Attainment

We used educational attainment as an indicator of SEP. We obtained educational attainment at Tromsø6 and categorized it in four levels: "primary/partly secondary education: (p to 10 years of

schooling)", "upper secondary education: (a minimum of 3 years)", "tertiary education, short (college/university less than 4 years)", and "tertiary education, long (college/university 4 years or more)". These correspond approximately to the International Standard Classification for Education (ISCED) 2011 levels 0-2 (up to 10 years of schooling), 3-4 (approximately 11-13 years), 5-6 (approximately 14-16 years) and 7-8 (17 years or more) (UNESCO Institute for Statistics, 2012). We replaced missing values at Tromsø6 with the attainment reported at Tromsø7 (n = 8), assuming educational attainment remains stable throughout mid and late adulthood and excluded seven individuals due to missing educational attainment at both waves.

In the main analysis, we treated educational attainment as an ordinal variable with a continuous score (1-4), since it allows the results to be interpreted as the association per one-level increase in education while reducing the number of tests performed across 52 outcomes and two waves. We evaluated divergence from this assumption by considering educational attainment as a four-level categorical variable in a sensitivity analysis (Section 2.7).

2.3. Inflammatory proteins

Non-fasting blood samples were drawn at each study visit into EDTA tubes, centrifuged, and plasma aliquots were stored at −70 °C until analysis. Participants received no specific instructions before attendance regarding food intake, smoking or physical activity, with samples being collected throughout the working day. Inflammatory protein levels were measured from plasma samples using the OLINK Target 96 Inflammation panel. This targeted method allows the simultaneous measurement of the concentration of 92 different proteins via Proximity Extension Assay (PEA). PEA uses antibody pairs, labelled with DNA oligonucleotides, to bind target proteins in the samples. If the oligonucleotides are brought into proximity, they hybridize and are later amplified using polymerase chain reaction. The readout is Normalized Protein Expression (NPX), which is a log2-transformed relative measurement of the proteins' concentration.

The analysis was executed in two batches (2019 and 2023) with 13 plates each. Four internal controls are spiked into each sample at the same concentration and an absolute deviation over 0.3 NPX in any of the controls leads to the sample failing the quality control (QC) assessment. Twenty-four samples from Tromsø6 and 29 from Tromsø7 failed individual QC and were excluded. Therefore, protein levels were available for 929 samples from Tromsø6 and 1,257 samples from Tromsø7. A total of 909 individuals had protein measurements from both waves and were considered as our main analytical sample (Fig. 1).

To detect background noise, negative controls are incorporated in each plate. Sample NPX levels below the protein concentration detected for the negative controls are marked as under the limit of detection (LOD). From the 92 proteins included in the panel, we filtered away 24 as they were reported as under the LOD in over 50% of the samples for Tromsø6 or Tromsø7. For the remaining 68 proteins, we imputed the values under the LOD for individuals with missing data using Quartile Regression for Left Censored Data with the library *imputeLCMD* (version 2.1) in R (Lazar & Burger, 2014) (Supplementary Table S1).

2.4.Data harmonization and batch effect

To address the batch effect for the Tromsø7 samples analyzed at 2019 and 2023, we randomly selected 36 samples analyzed in 2019 (first batch) and re-analyzed them in 2023 (second batch). Three of these samples did not pass the QC assessment at one or both batches, leaving 33 samples with paired protein measurements remaining.

We assessed the agreement between the protein levels from the samples analyzed in both batches using Bland-Altman analysis. For each protein and pair of measurements, we calculated and compared the mean of the protein levels and the difference between them. We identified outliers based on the agreement for each protein as pairs of measurements for which the difference in the protein levels was outside of the 95% confidence interval (CI) around the mean difference (Supplementary Fig. S2). Three samples were consistently outliers for over six proteins (10%) and were filtered out. We calculated the Spearman's rank correlation among the remaining paired samples for each protein and filtered out 16 proteins from the analysis due to low correlation ($\rho < 0.75$), which suggests low reproducibility (Supplementary Fig. S3). For the remaining 52 proteins, we used the median of the paired differences as a bridging factor, harmonizing the data from the two batches.

2.5. Covariates

We included age and sex as confounders in all analyses. Further, we considered several covariates comprising lifestyle factors such as smoking status (former, current, never), alcohol consumption frequency (never, once a month, 2-4 times a month, 2-3 times a week, more than 4 times a week), physical activity (less than once a week , once a week, 2-3 times a week, daily); BMI; prevalent health conditions including cardiovascular disease, diabetes, chronic pain, and psychological conditions; and medication use including cardiovascular disease medication, diabetes medication, and psychotropics during the four weeks prior to data collection.

Lifestyle factors, health conditions, and medication were obtained from self-reported questionnaires at each wave, while BMI was calculated as weight divided by height squared, based on the measured height and weight of the participants at each visit with no footwear and light clothing. The covariate dataset contained less than 2% missing values per wave, which were assumed to be missing at random and imputed using random forests using the *missForest* R package (version 1.5) (Stekhoven & Buehlmann, 2012)

2.6. Statistical analysis

We assessed the cross-sectional association between educational attainment and protein levels at each wave using univariate linear regression models with data from the individuals who had protein measurements at both waves ($n = 909$). In our main analysis, we used educational attainment adjusted for age and sex as confounders (Model 1). In the second model (Model 2), we further adjusted for BMI and lifestyle factors including daily smoking, alcohol consumption frequency, and physical activity. In the third model (Model 3), we included the same covariates as in Model 2 as well as prevalent cardiovascular disease, diabetes, chronic pain, psychological conditions, and related medication use.

To evaluate the longitudinal stability of the educational gradient in the protein levels, we later fit linear mixed models with a random intercept for each individual. We included age and sex as confounders and an interaction term between education and wave to determine whether the educational gradient was changing across waves. For the linear mixed models, all subjects and samples (with or without repeated measurements) were included to increase the statistical power (n = 929 at Tromsø6; n = 1,257 at Tromsø7).

We assessed nominal statistical significance at a threshold of 0.05 (p<0.05) and addressed multiple testing using false discovery rate (FDR) with the Benjamini–Hochberg procedure (Benjamini & Hochberg, 1995). We considered the associations under a threshold of 0.1 (FDR<0.1) as significant due to the exploratory nature of this study, which indicates that an estimated 90% of the significant associations are expected to be true positives. All the analyses were performed using R, version 4.4.1 (R Core Team, 2020).

2.7. Sensitivity Analyses

To assess potential selection bias, we compared baseline characteristics at Tromsø6 between individuals included in the analytical sample and those who attended Tromsø6 but were not included in the analysis, using chi-squared and Kruskal–Wallis tests. To investigate possible nonlinear associations, we repeated our main analysis treating educational attainment as a nominal variable with four levels: “primary/partly secondary”, “upper secondary”, “college/university less than 4 years”, and “college/university 4 years or more”. To maximize sample size, we performed cross-sectional analyses with all available samples that passed the QC at each wave (n = 929 at Tromsø6; n = 1,257 at Tromsø7). Additionally, because the bridging process can introduce bias, we repeated the cross-sectional analysis at Tromsø7 using only the data from the samples analyzed in 2019 (n = 1,144), without bridging, for individuals that had reported their educational attainment and whose analyzed samples had passed QC (n = 1,112). Moreover, we performed a sensitivity analysis stratifying the study population by sex.

To evaluate whether the association between educational attainment and inflammatory protein levels remained similar among participants with healthier lifestyle habits, we repeated our analyses among individuals with a BMI under 25 at each wave (n = 287 at Tromsø6; n = 267 at Tromsø7) and among never smokers (n = 327 at Tromsø6; n = 316 at Tromsø7). Finally, to investigate a potential cohort effect, we stratified the population into two groups by the median age at Tromsø6.

3. Results

3.1. Study population

The study population (n = 909) was older, contained a higher percentage of men, and had fewer smokers than the complete Tromsø6 cohort (Supplementary Table S2). Further, a higher proportion reported exercising once and two-three times per week, and higher alcohol consumption frequency compared to the complete Tromsø6 cohort. No significant difference was observed in educational attainment.

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The characteristics of the study population at Tromsø6, stratified by educational attainment, are presented in Table 1 (Tromsø7 in Supplementary Table S3). Upper Secondary education was the most prevalent level attained, while college/university under four years was the least represented. Individuals with the lowest educational attainment, primary/partly secondary, were more likely to be daily smokers, to have cardiovascular diseases, chronic pain, and to use cardiovascular medication. On the other hand, those with the highest educational attainment, college/university four years or more, reported higher frequency of physical activity and alcohol consumption, and had lower BMI.

We observed changes in lifestyle factors for the study population when comparing the habits at Tromsø6 and Tromsø7 (Supplementary Table S4). Specifically, the participants reported increased exercise frequency, less smoking, and higher alcohol consumption at Tromsø7. In addition, the average BMI was higher at Tromsø7.

3.2. Educational attainment and inflammatory proteins

Educational attainment was associated with the levels of eight proteins at one or both waves in linear regression models adjusted for age and sex (Model 1, FDR<0.1, Fig. 2, Table 2, Supplementary Table S5). At both waves, higher educational attainment was consistently associated with lower levels of C-C motif chemokine 20 (CCL20), CUB domain-containing protein 1 (CDCP1), and HGF, and higher levels of cystatin-D (CST5) (FDR<0.1). At Tromsø7 only, higher educational attainment was associated with lower levels of C-C motif chemokine 19 (CCL19), IL-6, and oncostatin-M (OSM), and higher levels of fibroblast growth factor 19 (FGF19) (FDR<0.1).

All the observed associations were attenuated after adjusting for lifestyle factors, BMI, health conditions, and medication use at both waves. At Tromsø6, the associations with CDCP1 and CST5 remained significant in Model 2, and CST5 and FGF19 in Model 3 (p<0.05; Fig. 3A, Supplementary Tables S6 and S7). At Tromsø7, CST5, IL-6, and OSM remained significant in Model 2, but only OSM in Model 3 (p<0.05; Fig. 3B, Supplementary Tables S6 and S7). However, none of the associations in Models 2 and 3 were statistically significant after adjusting for multiple testing at either wave (FDR<0.1).

3.3. Stability of the association between educational attainment and inflammatory proteins across both waves

The educational gradient in inflammatory protein levels persisted across waves, and no protein was significantly associated with the interaction term between education and wave in linear mixed models incorporating data from both waves (FDR<0.1, Table 2, Supplementary Table S8). We observed that higher educational attainment was associated with lower levels of CCL20 and CDCP1, consistent with cross-sectional findings, and with lower levels of CCL19 and CCL11 (FDR<0.1). Noteworthy, CCL11 was associated with educational attainment at Tromsø7 in the sensitivity analysis including all available samples (Supplementary Table S10).

3.4. Sensitivity Analyses

Similar results as in the main analysis were observed when treating educational attainment as a categorical variable, largely driven by the difference between the highest, college/university 4 years or more, and the lowest, primary/partly secondary education, levels. Specifically, individuals with the highest educational attainment had lower levels of CCL20, CDCP1, HGF, IL-6, and OSM, and higher levels of CST5 and FGF19 compared to those with the lowest educational attainment (Supplementary Fig. S4, Supplementary Table S9). The categorical estimates were therefore consistent with the ordinal estimates but suggest a threshold at tertiary education rather than uniform differences between the levels.

Five additional proteins were inversely associated with higher educational attainment at Tromsø7 when including all available samples: CCL11, interleukin-18 (IL-18), interleukin-18 receptor 1 (IL-18R1), osteoprotegerin (OPG), and TNFSF14 (FDR<0.1, Supplementary Fig. S5, Supplementary Table S10). In addition, we observed comparable coefficients for the proteins associated with education in the main analysis when considering only samples from Tromsø7 measured in 2019 (Supplementary Fig. S6, Supplementary Table S11). In sex-specific analysis, we observed similar trends and effect directions, with larger effect sizes for women in the levels of CCL20, and OSM, and for men in the levels of CCL19, FGF19, and IL-6 (Supplementary Fig. S7, Supplementary Table S12). There were no significant interactions between sex and education associated with protein levels (Supplementary Table S13).

Additionally, we restricted our study population to include only individuals with a BMI < 25 and never-smokers. The observed effect directions were consistent with our main analysis (FDR<0.1, Supplementary Figs. S8 and S, Supplementary Tables S14 and S15). After stratifying the study population by median age at Tromsø6, we observed consistent associations for both groups at Tromsø7, with a larger effect size for the younger group (FDR<0.1). However, there were age-related variations for OSM at Tromsø6, with an inverse association for the younger group and a positive association for the older group (FDR<0.1). Furthermore, in the younger group, several additional proteins were inversely associated with higher educational attainment (FDR<0.1, Supplementary Tables S16 and S17).

4. Discussion

In this study, we investigated the association between educational attainment and a panel of inflammatory proteins, measured for the same individuals at two time points (Tromsø6 and Tromsø7), seven to eight years apart. Higher educational attainment was associated with lower levels of CCL20, CDCP1, and HGF, and higher levels of CST5 at both waves. In addition, higher educational attainment was associated with lower levels of CCL19, IL-6, and OSM, and higher levels of FGF19 at Tromsø7 only. All the associations were attenuated after adjusting for covariates at both waves and only retained nominal significance. In longitudinal models, we observed no evidence that the educational gradient changed across waves, and an association between higher educational attainment and lower levels of CCL11, CCL19, CCL20, and CDCP1.

Socioeconomic differences in systemic inflammation have been consistently documented, primarily through higher plasma levels of cytokines (e.g. IL-6, Tumor Necrosis Factor- alpha) and acute-phase proteins (e.g. CRP, fibrinogen) among individuals in disadvantaged SEP including lower educational attainment, manual occupation or lower income (Davillas et al.,

2017; Fraga et al., 2015; Muscatell et al., 2020). Consistently, we observed higher levels of IL-6 and OSM among individuals with lower educational attainment. Both proteins are cytokines that stimulate the induction of other inflammatory proteins and have been associated with increased cardiovascular disease risk and mortality (Bernard et al., 1999; Chen et al., 2018; Gémes et al., 2008). We observed similar associations with CCL20, CCL19, and CCL11, which are chemokines involved in the migration and accumulation of immune cells. Higher levels among individuals with lower educational attainment could reflect an increased chemotactic activity, which can contribute to systemic inflammation (Dieu et al., 1998; Luster et al., 2005). Furthermore, lower educational attainment is associated with greater exposure to chronic psychosocial stressors including economic strain, adverse working conditions and lower perceived social status. These stressors may contribute to the observed pattern through sustained activation of the hypothalamic–pituitary–adrenal axis and glucocorticoid resistance, which impairs the anti-inflammatory regulation of chemokines (Rohleder, 2019).

In addition, higher levels of CDCP1 and HGF have been observed among individuals with lower area-level SEP, acting as mediators between SEP and cardiovascular disease in adult women (Lin et al., 2025). Although Lin et al. used an area-level socioeconomic indicator, the association remained consistent, showing higher CDCP1 and HGF levels among those in disadvantaged positions. Further, higher levels of CDCP1 in plasma have been associated with increased risk of lung cancer and poor prognosis for breast, lung, kidney, and liver cancer (Awakura et al., 2008; Dagnino et al., 2021; Ikeda et al., 2009; Miyazawa et al., 2010; Turdo et al., 2016). Taken together, these results highlight a link between lower educational attainment and higher plasma levels of proteins associated with higher risk of cardiovascular disease and cancer, and poor cancer prognosis.

In contrast, higher educational attainment was associated with higher levels of CST5 and FGF19. CST5 is a cysteine protease inhibitor with tissue-remodeling properties regulated by vitamin D3. Vitamin D has been observed to be influenced by sunlight exposure, supplement use, fatty fish consumption, and sun-seeking holidays during the limited winter daylight of Northern Norway (Brustad et al., 2007). We hypothesize that differences in these behaviors by educational attainment could explain the observed association. On the other hand, FGF19 is a protein involved in glucose tolerance and bile acid regulation (Ryan et al., 2013); its levels fluctuate over the course of the day and rise after food intake (Lundåsen et al., 2006). Since the protein levels in this study were measured in non-fasting blood samples collected throughout the day, the observed association might potentially be influenced by dietary patterns and time of blood collection.

All associations between educational attainment and inflammatory protein levels were substantially attenuated after accounting for lifestyle factors and BMI. The further adjustment for prevalent health conditions and medication led only to marginal attenuation. Higher educational attainment is associated with higher health literacy and healthier behaviors, possibly leading to lower BMI, less smoking, and greater physical activity, which are associated with lower systemic inflammation (Chang et al., 2021; Levitzky et al., 2008; Liu et al., 2017; Muscatell et al., 2020). These lifestyle factors are themselves partially shaped by constrained access to health-promoting resources, rather than reflecting individual choice alone (Lawrence, 2017). These results,

together with the literature indicate that lifestyle factors are possible mediators between educational attainment and inflammation. However, the design and analysis in our study are not appropriate to quantify the mediating contribution.

We did not observe significant changes in the educational gradient in inflammatory protein levels between the two waves. Previous research has reported stable socioeconomic gradients in IL-6 and CRP over time when considering occupation as an indicator of SEP (Gimeno et al., 2007). Healthy adults show low intra-individual variation in inflammatory protein levels (Brodin & Davis, 2017), suggesting an established baseline shaped in part by early-life social conditions (Lockwood et al., 2018). Disadvantaged early-life SEP has been linked to persistently higher IL-6 levels in adults, with educational attainment identified as a stronger mediator of this relationship compared to occupation and income (Berger et al., 2019; Carmeli et al., 2020).

On the other hand, we did not observe an educational gradient in the levels of traditional inflammatory markers like Tumor Necrosis Factor alpha (TNF), Monocyte Chemoattractant Protein-1 (MCP1), and Interferon Gamma (IFNG) at either wave. While previous studies have reported socioeconomic gradients among the levels of these proteins, the evidence is inconsistent (Fraga et al., 2015; Lin et al., 2025; Maurel et al., 2020). One potential reason for not detecting these gradients could be that the effect may be too small to detect in our sample size. These small effects could in turn reflect the highly egalitarian Norwegian setting. Norway has overall low inequality compared to other high- and middle-income countries (Aaberge et al., 2020; OECD, 2025; Thévenot, 2017). One study performed using data from four European countries reported that the differences in systemic inflammation between advantaged and disadvantaged SEP groups were smaller in countries with lower inequality (Layte et al., 2019). While our results show that the educational gradient in systemic inflammation persists in highly egalitarian settings, the small effect sizes and lack of associations among some proteins suggest that some of the effect may be partially buffered. Nonetheless, the participants of the Tromsø Study have, on average, higher educational attainment than the residents of Tromsø, who in turn have higher educational attainment than the general population of Norway (Statistics Norway, 2026; Vo et al., 2023). Therefore, the magnitude of the associations we observed may not transfer to other settings.

The main strength of this study was the use of repeated protein measurements. Using two measurements from the same individuals allowed us to observe the association between educational attainment and inflammatory protein levels at two waves and detect whether the educational gradient in the protein levels was stable across the two waves. In addition, the protein panel enabled exploration of multiple inflammatory proteins beyond cytokines and acute-phase proteins. However, some limitations remain in this study. First, educational attainment is a single indicator of SEP and does not precisely capture income, wealth, occupational exposures, or material living conditions. Second, our study population was sampled from a population-based study, where healthy individuals are more likely to participate, and the selection of participants from those that attended two waves of the same study might introduce survivor bias: our sample was older, more often male, and less often smokers than the full Tromsø6 cohort. In addition, our sample could differ from the individuals lost to follow-up, who participated Tromsø6 but not Tromsø7. Third, while self-reported educational attainment has been validated in the Tromsø

Study (Vo et al., 2023), lifestyle factors, health conditions, and medication use were also self-reported, introducing the potential for misclassification and recall bias. Fourth, the plasma samples were stored in the freezer for different time periods before analysis, which can affect protein concentration. In addition, NPX values are relative rather than absolute measurements of protein expression levels, which hinders the possibility to categorize or filter proteins and individuals according to clinical cut-offs. Finally, due to the low correlation among the protein levels of samples that were tested at the two batches and observations under LOD, we had to reduce the number of proteins from 92 to 52.

5. Conclusions

We found a consistent association between higher educational attainment and lower levels of CCL20, CDCP1, HGF, and higher levels of CST5 at two time points, seven to eight years apart, with no evidence that these associations changed over this period. The persistent associations imply a potential effect of education over processes such as cell growth, tissue remodeling, and cell migration, through proteins associated with increased risk of cardiovascular diseases and cancer. Adjusting for lifestyle factors and BMI substantially attenuated these associations, highlighting the relevance of modifiable risk factors and their potential as intervention targets for reducing the persistent socioeconomic gradient in systemic inflammation.

Data availability

The Tromsø Study is available upon reasonable request to researchers who have obtained approval from the Data and Publication Committee of the Tromsø Study. More information is available at https://uit.no/research/tromsostudy.

Ethics Declaration

All participants of the Tromsø Study provided informed consent prior to their participation. The Tromsø Study complies with the 1964 Declaration of Helsinki and has received approval from the Regional Committee for Medical and Health Research Ethics (REK) in Northern Norway (Ref. 2009/2536 for Tromsø6, and Ref. 2014/940 for Tromsø7). In addition, REK approval was granted for this research project (Ref. 817197).

Competing Interests

The authors declare that they have no conflict of interests that could have influenced the development of this study. MCH holds shares in the company O-SMOSE and has no conflict of interest to disclose. All consulting activities conducted by the company are independent of the present work.

Acknowledgements

EHF and LN are supported by the Healthy Choices project, funded by the Research Council of Norway (grant number 289440). The funders had no influence on the present study.

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CRediT Authorship Contribution Statement

Julian Otero: Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Software, Visualization, Writing – original draft, Writing – review and editing. **Ilona Urbarova:** Conceptualization, Methodology, Investigation, Supervision, Writing – original draft, Writing – review and editing. **Tom Wilsgaard:** Conceptualization, Funding acquisition, Methodology, Investigation, Supervision, Writing – original draft. **Hélène Colineaux:** Data Curation, Writing – review & editing. **Therese Haugdahl Nøst:** Writing – review & editing. **Raphaële Castagné:** Writing – review & editing. **Christopher Sivert Nielsen:** Resources, Writing – review & editing. **Lola Neufcourt:** Writing – review & editing**. Sameline Grimsgaard:** Writing – review & editing. **Dragana Vuckovic:** Writing – review & editing. **Marc Chadeau-Hyam:** Conceptualization, Funding acquisition, Writing – review & editing. **Cyrille Delpierre:** Conceptualization, Funding acquisition, Writing – review & editing. **Michelle Kelly-Irving:** Conceptualization, Funding acquisition, Writing – review & editing. **Torkjel M. Sandanger:** Conceptualization, Funding acquisition, Writing – review & editing**. Erlend Hoftun Farbu:** Conceptualization, Funding acquisition, Methodology, Investigation, Supervision, Project administration, Writing – original draft, Writing – review and editing.

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Figure Caption

Fig. 1. Flowchart of participants' selection and inflammatory protein level measurements*. 955 individuals had protein measurements at both waves, while 338 only had them at Tromsø7. After exclusion based on missing exposure (educational attainment) and quality control, 929 individuals had protein levels available at Tromsø6 and 1,257 at Tromsø7, with 909 overlapping and having protein levels available at both waves.*

Fig. 2. The association between education and inflammatory protein levels*. The regression coefficients and p-values for education are calculated from linear regression models adjusted for age and sex at Tromsø6 (a) and Tromsø7 (b). Horizontal lines indicate the p-value threshold (0.05) and the FDR threshold (0.1). Significant associations at each wave are shown in black ($p<0.05$). Associations that remained significant after adjusting for multiple testing (FDR<0.1) only at Tromsø7 are marked in teal, and those that remained at both waves are marked in red.*

Fig. 3. The association between education and inflammatory protein levels after adjusting for lifestyle factors, BMI, health conditions, and medication use*. The regression coefficients and 95% confidence intervals (CI) for education are calculated from linear regression models with education as the independent variable at Tromsø6 (a) and Tromsø7 (b). Model 1 was adjusted for age and sex (green). Model 2 was further adjusted for BMI, smoking status, alcohol consumption frequency, and physical activity (blue). Model 3 was further adjusted for prevalent cardiovascular disease, diabetes, psychological conditions, chronic pain, and related medication (red). Only proteins significantly associated with education after adjusting for multiple testing (FDR<0.1) at one or both waves are shown.*

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Table Captions

Table 1. Characteristics of the study population at Tromsø6

Table 2. Cross-sectional and longitudinal associations between educational attainment and inflammatory protein levels. *Regression coefficients and 95% confidence intervals (CI) for educational attainment from cross-sectional linear regression models at Tromsø6 and Tromsø7, and from linear mixed models incorporating repeated measurements from both waves. Cross-sectional models were adjusted for age and sex. Mixed models were adjusted for age, sex, and wave, and included a random intercept per participant and an interaction term between educational attainment and wave. Only proteins significantly associated with educational attainment in at least one model after correction for multiple testing (FDR<0.1) are shown. Bold coefficients indicate significant associations (FDR<0.1).*

Highlights

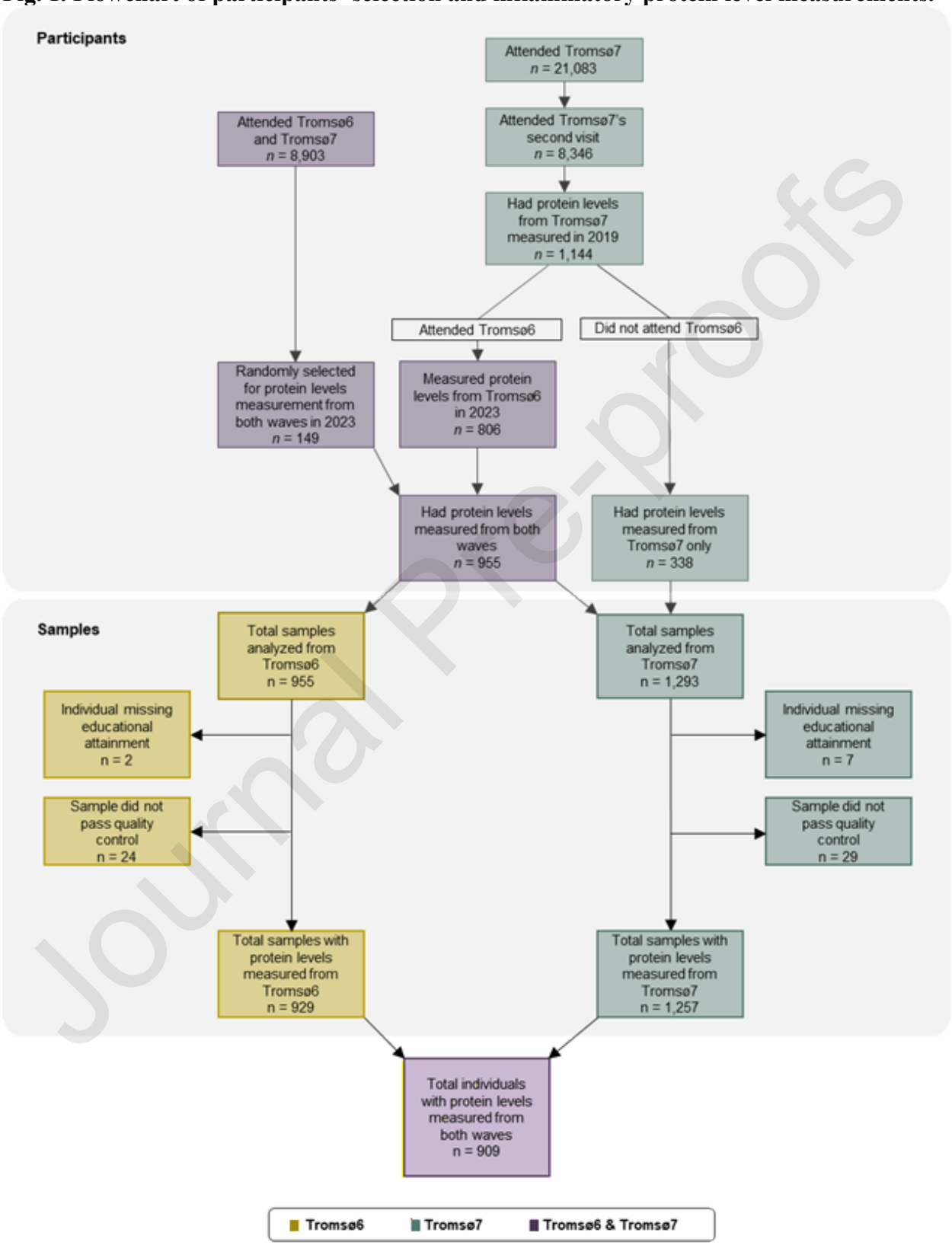
- Lower educational attainment is consistently associated with higher levels of CCL20, CSCP1, HGF, and lower levels of CST5 at two time points.
- Educational gradients in inflammatory protein levels remained stable over a seven-to-eight-year follow-up period.
- Lifestyle factors and body-mass index substantially attenuated the association between educational attainment and systemic inflammation.
- Findings support the embodiment of socioeconomic disadvantage through systemic inflammation across adulthood.

Figures

Otero J. et al. – Educational attainment and systemic inflammation: evidence of a stable gradient from two measurements in the Tromsø Study (2007-2016)

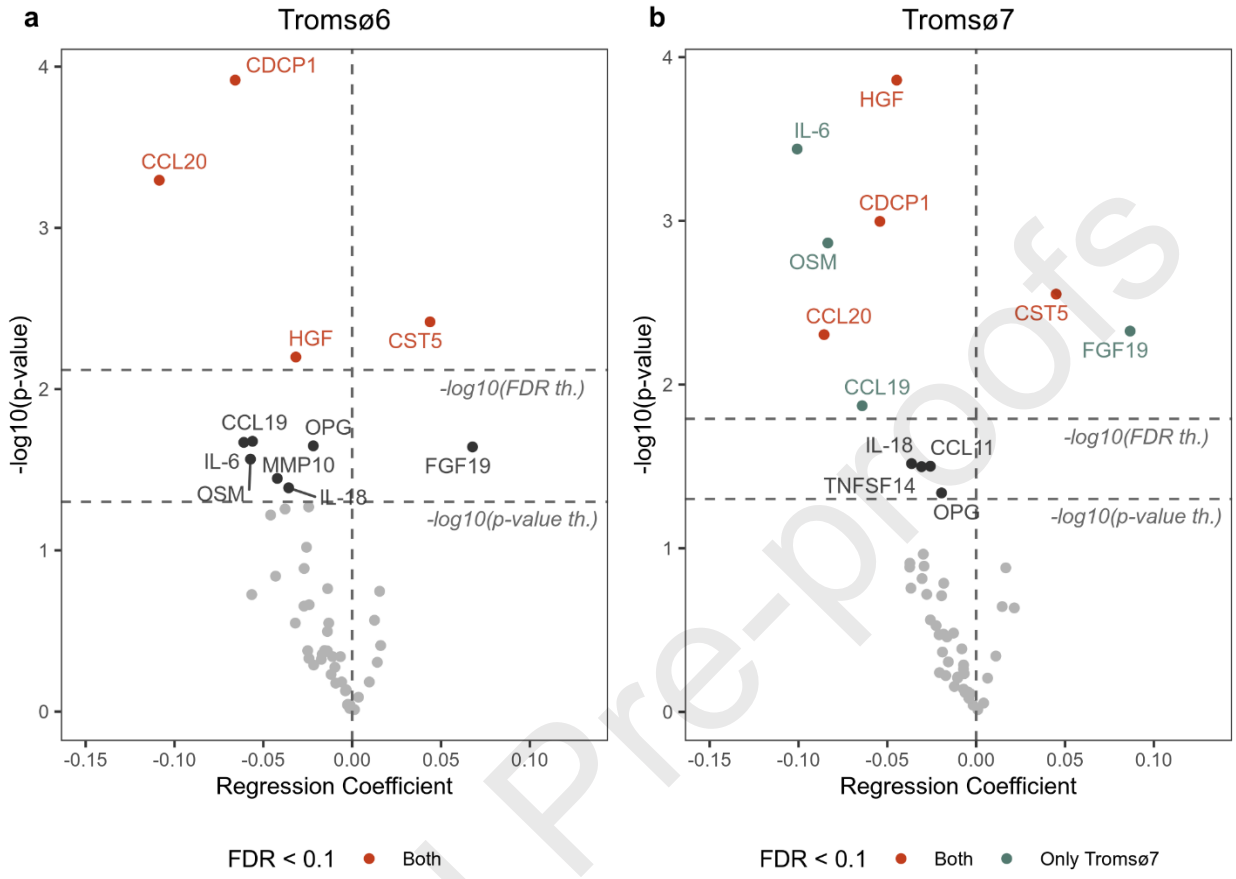
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Fig. 1. Flowchart of participants' selection and inflammatory protein level measurements.



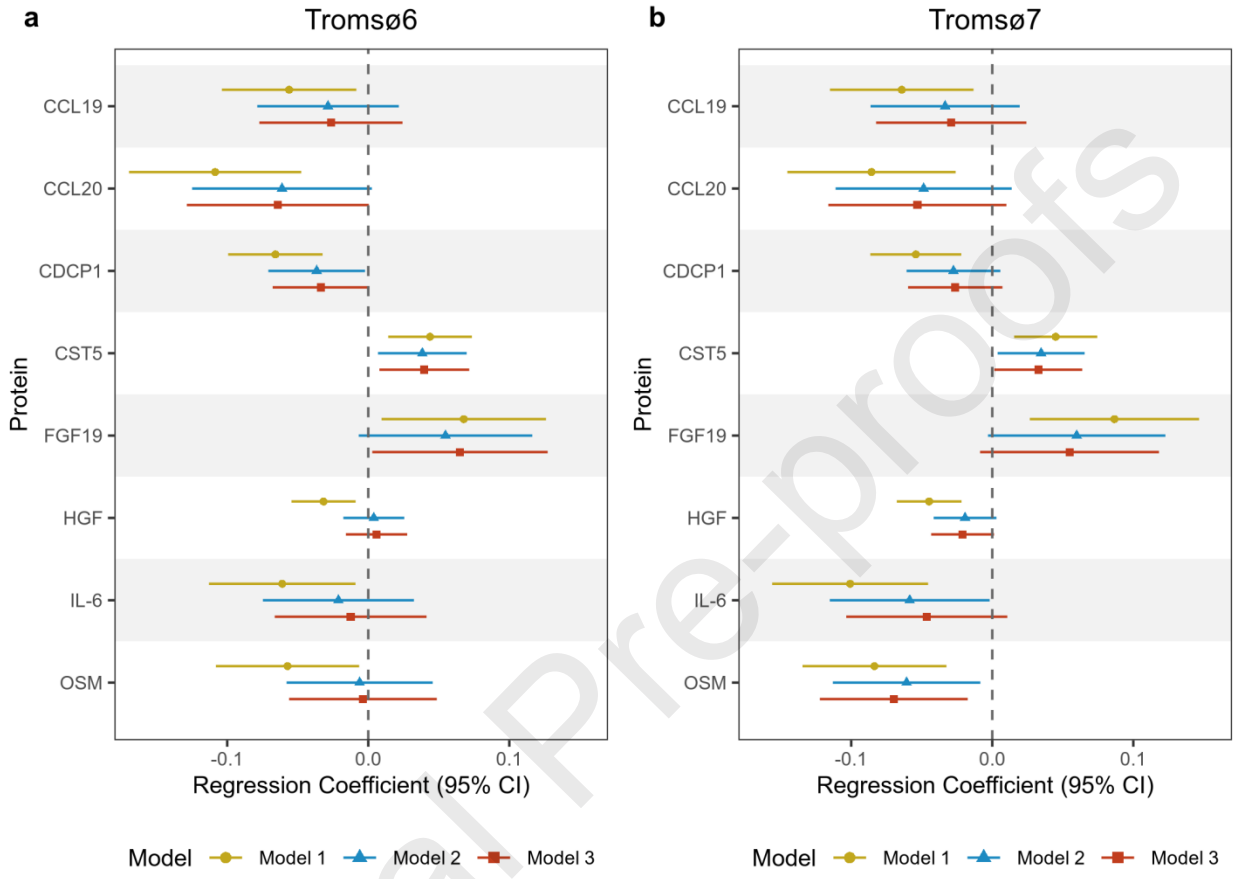
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Fig. 2. The association between education and inflammatory protein levels.



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Fig. 3. The association between education and inflammatory protein levels after adjusting for life-style factors, health conditions, and medication use.



Tables

Otero J. et al. – Educational attainment and systemic inflammation: evidence of a stable gradient from two measurements in the Tromsø Study (2007-2016)

Table 1. Characteristics of the study population at Tromsø6

	Total	**1: Primary/ partly secondary**	**2: Upper Secondary**	**3: University < 4 years**	**4: University >= 4 years**	**p-value***
Variable	(*n* = 909)	(*n* = 226, 24.9%)	(*n* = 320, 35.2%)	(*n* = 178, 19.6%)	(*n* = 185, 20.3%)	

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Age [years (SD)]	58.4 (9.2)	61.8 (8.1)	58.5 (8.8)	56.7 (9.6)	55.7 (9.4)	<0.001
Sex [n (%)]						<0.001
Female	449 (49.4%)	136 (60.2%)	161 (50.3%)	65 (36.5%)	87 (47.0%)	
BMI [kg/m^2 (SD)]	26.9 (3.8)	27.1 (3.6)	27.0 (3.6)	27.1 (3.9)	26.3 (4.1)	0.03
Exercise Frequency [n (%)]						<0.001
Less than weekly	163 (17.9 %)	56 (24.8 %)	63 (19.7 %)	35 (19.7 %)	9 (4.9 %)	
Once a week	224 (24.6%)	54 (23.9%)	74 (23.1%)	36 (20.2%)	60 (32.4%)	
2-3 times a week	372 (40.9%)	87 (38.5%)	138 (43.1%)	74 (41.6%)	73 (39.5%)	
Approximately every day	152 (16.7%)	31 (13.7%)	45 (14.1%)	33 (18.5%)	43 (23.2%)	
Alcohol Consumption Frequency [n (%)]						<0.001
Never	59 (6.5%)	22 (9.7%)	24 (7.5%)	8 (4.5%)	5 (2.7%)	
Monthly or less frequently	221 (24.3%)	76 (33.6%)	81 (25.3%)	31 (17.4%)	33 (17.8%)	
2-4 times a month	361 (39.7%)	92 (40.7%)	131 (40.9%)	83 (46.6%)	55 (29.7%)	
2-3 times a week	210 (23.1%)	31 (13.7%)	69 (21.6%)	44 (24.7%)	66 (35.7%)	

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4 or more times a week	58 (6.4%)	5 (2.2%)	15 (4.7%)	12 (6.7%)	26 (14.1%)	
Smoking status [n (%)]						<0.001
Never	327 (36.0%)	65 (28.8%)	98 (30.6%)	74 (41.6%)	90 (48.6%)	
Yes, now	153 (16.8%)	49 (21.7%)	62 (19.4%)	26 (14.6%)	16 (8.6%)	
Yes, previously	429 (47.2%)	112 (49.6%)	160 (50.0%)	78 (43.8%)	79 (42.7%)	
Cardiovascular disease [n (%)]						0.004
No	617 (67.9%)	132 (58.4%)	222 (69.4%)	128 (71.9%)	135 (73.0%)	
Yes	292 (32.1%)	94 (41.6%)	98 (30.6%)	50 (28.1%)	50 (27.0%)	
Diabetes [n (%)]						0.18
No	873 (96.0%)	219 (96.9%)	308 (96.3%)	166 (93.3%)	180 (97.3%)	
Yes	36 (4.0%)	7 (3.1%)	12 (3.8%)	12 (6.7%)	5 (2.7%)	
Psychological conditions [n (%)]						0.11
No	839 (92.3%)	208 (92.0%)	303 (94.7%)	164 (92.1%)	164 (88.6%)	
Yes	70 (7.7%)	18 (8.0%)	17 (5.3%)	14 (7.9%)	21 (11.4%)	
Chronic Pain [n (%)]						<0.001

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No	679 (74.7%)	151 (66.8%)	231 (72.2%)	145 (81.5%)	152 (82.2%)	
Yes	230 (25.3%)	75 (33.2%)	89 (27.8%)	33 (18.5%)	33 (17.8%)	
Heart Medication [n (%)]						0.001
Not used	613 (67.4%)	130 (57.5%)	217 (67.8%)	131 (73.6%)	135 (73.0%)	
Yes, now or previously	296 (32.6%)	96 (42.5%)	103 (32.2%)	47 (26.4%)	50 (27.0%)	
Diabetes medication [n (%)]						0.47
Not used	879 (96.7%)	219 (96.9%)	310 (96.9%)	169 (94.9%)	181 (97.8%)	
Yes, now or previously	30 (3.3%)	7 (3.1%)	10 (3.1%)	9 (5.1%)	4 (2.2%)	
Psychotropics in the past 4 weeks [n (%)]						0.14
Not used	878 (96.6 %)	213 (94.2 %)	312 (97.5 %)	172 (96.6 %)	181 (97.8 %)	
Yes	31 (3.4 %)	13 (5.8 %)	8 (2.5 %)	6 (3.4 %)	4 (2.2 %)	

* p-values were calculated using a Chi-squared test for categorical variables, and Kruskal-Wallis test for continuous variables.

Table 2. Cross-sectional and longitudinal associations between educational attainment and inflammatory protein levels.

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	Tromsø6		Tromsø7		Mixed-Model			
	Education		Education		Education		Education x Wave	
Protein	**Coeff.**	**95% CI**	**Coeff.**	**95% CI**	**Coeff.**	**95% CI**	**Coeff.**	**95% CI**
CCL11	-0.024	(-0.049, 3.99E-04)	-0.026	(-0.049, -0.002)	**-0.034**	**(-0.056, -0.011)**	0.007	(-0.013, 0.028)
CCL19	-0.056	(-0.104, -0.008)	**-0.064**	**(-0.115, -0.013)**	**-0.067**	**(-0.112, -0.021)**	-0.011	(-0.047, 0.025)
CCL20	**-0.109**	**(-0.170, -0.048)**	**-0.086**	**(-0.145, -0.026)**	**-0.104**	**(-0.160, -0.048)**	0.016	(-0.038, 0.071)
CDCP1	**-0.066**	**(-0.099, -0.032)**	**-0.054**	**(-0.086, -0.022)**	**-0.063**	**(-0.092, -0.033)**	0.005	(-0.019, 0.029)
CST5	**0.044**	**(0.014, 0.073)**	**0.045**	**(0.016, 0.074)**	0.031	(0.005, 0.057)	-0.004	(-0.024, 0.016)
FGF19	0.068	(0.009, 0.126)	**0.087**	**(0.027, 0.147)**	0.063	(0.008, 0.119)	-9.19E-04	(-0.060, 0.059)
HGF	**-0.032**	**(-0.054, -0.009)**	**-0.045**	**(-0.068, -0.022)**	-0.027	(-0.049, -0.006)	-0.019	(-0.039, 5.22E-04)
IL-6	-0.061	(-0.113, -0.009)	**-0.101**	**(-0.156, -0.046)**	-0.056	(-0.106, -0.005)	-0.051	(-0.096, -0.006)
OSM	-0.057	(-0.108, -0.006)	**-0.084**	**(-0.135, -0.032)**	-0.044	(-0.092, 0.004)	-0.022	(-0.069, 0.026)

Journal Pre-proofs