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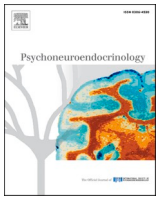

Educational patterning in biological health seven years apart: Findings from the Tromsø Study

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ABSTRACT

Background: Social-to-biological processes is one set of mechanisms underlying the relationship between social position and health. However, very few studies have focused on the relationship between social factors and biology at multiple time points. This work investigates the relationship between education and the dynamic changes in a composite Biological Health Score (BHS) using two time points seven years apart in a Norwegian adult population.

Methods: We used data from individuals aged 30 years and above who participated in Tromsø6 (2007–2008) and Tromsø7 (2015–2016) (n = 8117). BHS was defined using ten biomarkers measured from blood samples and representing three physiological systems (cardiovascular, metabolic, inflammatory). The higher the BHS, the poorer the health status.

Findings: Linear regression models carried out on BHS revealed a strong educational gradient at two distinct time points but also over time. People with lower educational attainment were at higher risk of poor biological health at a given time point ($\beta_{\text{low education Tromsø6}}$=0.30 [95 %-CI=0.18–0.43] and $\beta_{\text{low education Tromsø7}}$=0.30 [95 %-CI=0.17–0.42]). They also presented higher longitudinal BHS compared to people with higher education ($\beta_{\text{low education}}$ = 0.89 [95 %-CI=0.56–1.23]). Certain biomarkers related to the cardiovascular system and the metabolic system were strongly socially distributed, even after adjustment for sex, age, health behaviours and body mass index.

Conclusion: This longitudinal analysis highlights that participants with lower education had their biological health deteriorated to a greater extent over time compared to people with higher education. Our findings provide added evidence of the biological embodiment of social position, particularly with respect to dynamic aspects for which little evidence exists.

1. Introduction

Evidence has accumulated on the relationship between social inequalities and health inequalities. A more disadvantaged social position whether assessed by income, education or occupation has been associated with a higher rate of many health conditions and diseases, and a social gradient in health starts early in life (Ben-Shlomo and Kuh, 2002; Gallo et al., 2012). However, the potential processes and mechanisms that may underlie the observed associations still need to be better understood. The social-to-biological transition is one set of mechanisms underlying the relationship between social position and health (Blane et al., 2013; Kelly-Irving and Delpierre, 2021). This refers to the concept of embodiment (Krieger, 2005), which postulates that the human environment and its associated physical, chemical and psychosocial stressors trigger psychological, behavioural and biological adaptative processes along the life course. Specifically, social environments may influence health through two main types of initial exposures that are socially distributed: First, 'exogenous' exposures which include

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environmental exposures such as pollution, pesticides, work exposures and behaviours such as tobacco, alcohol, diet. Second, 'endogenous' exposures (especially psychosocial exposures) that imply subjective interpretation and "internal" molecular responses from the body mainly linked to stress perception and stress response systems likely to modify the biology. A growing body of research supports the notion that lifelong exposure to stressful situations causes physiological dysregulation that subsequently manifests as disease through persistent activation of the stress response systems (McEwen and Stellar, 1993). Allostasis is the process through which our body adjusts to difficult or stressful external circumstances in order to preserve physiological equilibrium (McEwen and Wingfield, 2003). Allostatic load (AL) has been proposed as a measure of overall physiological wear-and-tear which results from the repetitive activation of compensatory physiological systems in response to environmental challenges and chronic physiological stress (Delpierre et al., 2016; Juster et al., 2010; McEwen and Stellar, 1993; Seeman et al., 1997), and has been linked to subsequent morbidity and mortality (Barboza Solís et al., 2016; Castagné et al., 2018). In addition, an association between disadvantaged socioeconomic position and higher AL has been reported in the literature (Johnson et al., 2017).

AL raises questions of operationalization. AL was primarily developed to measure the physiological response to stress and originally included ten biomarkers from four biological domains: hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system, cardiovascular system and metabolic system (Seeman et al., 1997). However, in their review, Johnson et al. reported that there was a substantial inconsistency in biomarkers used to build the AL but also a poor fidelity to its original conception (Johnson et al., 2017). Beyond the field of social epidemiology, AL has laid out and operationalised the idea that multiple biological systems are involved in how humans respond to the challenges of their environment, which in turn influences multiple health outcomes related to aging. This has led to broadening the incorporation of various aspects of biological processes into summarizing physiological changes with age (Levine, 2013; Belsky et al., 2015; Crimmins, 2020). Recently, some authors have proposed to analyse biological health scores (BHS) to highlight the discrepancy with the original definition of AL. Consistent with the theory of AL, this composite score aims to measure a multisystem dysregulation by integrating a wider array of biomarkers to represent more physiological systems than those originally found in AL, such as liver and kidney functions, inflammatory and immune systems (Seeman et al., 2010; Karimi et al., 2019; Chadeau-Hyam et al., 2020). In practice, there is no gold standard (Delpierre et al., 2016; Johnson et al., 2017) and the measure of physiological wear-and-tear used is often data dependent.

To date, although several studies have examined the relationship between socioeconomic position and multisystem dysregulation (via AL or BHS) at specific time points (Hickson et al., 2012; Robertson et al., 2014; Karimi et al., 2019), very few have considered the relationship between social position and the dynamic changes in physiological wear-and-tear at different time points and over the life course, probably due to the complexity of obtaining such data. Nonetheless, analysing physiological wear-and-tear over time is important as longitudinal data provide a more comprehensive way of measuring cumulative physiological dysregulation. In addition, this may help us understand when and how social differences emerge, and if they are reversible. We identified seven published studies with several measures of AL, among which three reported a steeper increase of AL over time among people with lower socioeconomic position (Upchurch et al., 2015; Graves and Nowakowski, 2017; van Deurzen and Vanhoutte, 2019); one reported an association between a higher level of education and a slower increase in AL over time but only among participants with lower AL at baseline (Merkin et al., 2014); and three reported no association between socioeconomic position and change in AL over time (Chyu and Upchurch, 2018; Merkin et al., 2020; Richards et al., 2023). Of note, all the seven studies were conducted in specific groups of population (women only (Upchurch et al., 2015; Chyu and Upchurch, 2018) or adults over 45 years old (Merkin et al., 2014; Graves and Nowakowski, 2017; van Deurzen and Vanhoutte, 2019; Merkin et al., 2020; Richards et al., 2023)) but none in the general population in terms of age and sex. In addition, the seven studies also differed according to 1) the number (from 8 to 11) and 2) the nature of the variables included in the AL, as well as 3) the methodology for computing AL: five used the high-risk quartile method (Chyu and Upchurch, 2018; Graves and Nowakowski, 2017; Richards et al., 2023; Upchurch et al., 2015; van Deurzen and Vanhoutte, 2019) and two used scores standardized relatively to clinical cut-offs (Merkin et al., 2020, 2014); 4) the modelling of change in AL: four used latent growth curves models (Merkin et al., 2020, 2014; Upchurch et al., 2015; van Deurzen and Vanhoutte, 2019), two used Poisson regressions (Chyu and Upchurch, 2018; Graves and Nowakowski, 2017) and the last one used within-between panel regression models (Richards et al., 2023); 5) the nature of the indicator of socioeconomic position and **6)** the set of confounders and potential mediators considered. In particular, none of the seven studies have looked at the contribution of health behaviours, although they have been identified as potential mediators of the relation between the social environment and health in the literature (Petrovic et al., 2018).

Educational attainment may be used as a measure of social position which captures childhood cultural capital as well as social position in early adulthood, and is associated with health literacy, socio-economic status, social class and material circumstances (Khalatbari-Soltani et al., 2022). Using the Tromsø Study, we built a composite BHS as an outcome measure based on the AL theory of physiological dysregulation. The aim of the present work is to examine the association between education and BHS longitudinally using two time points seven years apart, and to explore the social patterning of each biomarker constituting the BHS at both waves in a Norwegian adult population. Our hypothesis is that cohort members with a lower educational attainment are more likely to experience elevated physiological wear-and-tear at each time point respectively, but also to exhibit higher cumulative physiological wear-and-tear over time. We also investigate the role of lifestyle factors in this association.

2. Methods

2.1. Study population

The Tromsø Study is a longitudinal population-based, prospective cohort study with repeated health surveys conducted since 1974 in the municipality of Tromsø, which is the largest city in Northern Norway. Based on the official population registry, Tromsø residents were invited by personal mail to take part in the survey. The design and data collection of the Tromsø Study are described in detail elsewhere (Jacobsen et al., 2012; Hopstock et al., 2022). The present paper is based on data from the sixth wave (Tromsø6) conducted in 2007/08 (N = 12, 984, aged 30 and above), and the seventh wave (Tromsø7) conducted in 2015/16 (N = 21,083, aged 40 and above). Attendance was around 65 % for both waves. Eligible participants were those who attended both Tromsø6 and 7 (N = 8906). We obtained anonymised individual-level data from both the health examination surveys and the questionnaires. An English translation of the questionnaires is available at the Tromsø Study homepage (http://www.tromsostudy.com).

The Tromsø Study was approved by the Data Inspectorate of Norway and the Regional Committee of Medical and Health Research Ethics, North Norway. Participation was voluntary and each subject gave written informed consent prior to participation.

2.2. Biological Health Score (BHS)

We constructed the BHS as a composite measure using a set of biomarkers. According to the physiological wear-and-tear theory, three types of biomarkers can be distinguished: primary biomarkers which are the biomarkers at the origin of the stress response cascade; secondary

biomarkers which reflect the cumulative outcome in response to the primary biomarkers in a specific organ or tissue; and tertiary biomarkers which are actual diseases or disorders (McEwen and Seeman, 1999). Among biomarkers available in the Tromsø Study dataset and based on existing literature on AL (McCrory et al., 2023; Seeman et al., 2010, 1997), we selected those available at both Tromsø6 and 7 (n = 10) which related to three of the most commonly represented systems in the AL literature: the cardiovascular, metabolic and inflammatory systems. Specifically, we included systolic, diastolic blood pressure and pulse rate (cardiovascular system); total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, glucose and glycated haemoglobin (HbA1C) (metabolic system); and C-reactive protein (CRP) (inflammatory system). These biomarkers are considered as secondary biomarkers. We chose to exclude BMI from biomarkers constituting the BHS because we considered it as a proxy for the outcome of previous lifestyle/ health behaviours (tertiary biomarker) (McEwen and Seeman, 1999).

Systolic and diastolic blood pressure as well as heart rate were measured using an automated Dinamap Pro care 300 Monitor (GE Healthcare, Norway). The cuff was chosen after the circumference of the upper arm was measured. Three readings on the upper right arm were taken in a sitting position at 1-min intervals and after a 2-min seated rest. We used the average of the last two measurements. Non-fasting blood samples were collected by venepuncture performed with subjects in a sitting position. Serum total cholesterol and triglycerides were analysed within 10 h by an enzymatic colorimetric method and HDL-cholesterol was analysed by a homogeneous enzymic colorimetric method. CRP was analysed by a highly sensitive CRP method (particle-enhanced immunoturbidimetric assay). The three analyses were performed on a Modal PPE auto-analyser with reagents from Roche Diagnostics Norway AS. Determinations of HbA1c were performed the next day on blood samples collected in EDTA anticoagulation vessels, determined by high-performance liquid chromatography (HPLC) using an automated analyser (Variant II, Bio-Rad Laboratories, Hercules, CA, USA) (Eggen et al., 2013, 2014; Hopstock et al., 2022).

The BHS was calculated using the sample distribution of each biomarker for each wave separately. Each biomarker was dichotomized into high versus low risk according to sex- and age-specific quartiles (Seeman et al., 1997). For age, we dichotomized the variable and considered 60 years old as a relevant cut-off both from a statistical (sufficient number of participants per group) and clinical perspective. A participant was considered to be 'at risk' for a given biomarker if the measured value of that biomarker was in the 4th quartile (1st quartile for HDL) of the empirical distribution of that biomarker in the sex- and age-specific group the individual belonged to. If the participant was defined as being 'at risk' for a given biomarker, they were attributed a subscore of 1 for that particular biomarker and 0 otherwise. For each participant, the BHS was then computed by summing biomarker-specific scores across all biomarkers. The BHS reflects the level of biological risk per age group and sex and ranges theoretically from 0 to 10. A higher BHS indicates increased biological risk across biomarkers, and therefore an increased susceptibility to poor health. This construction of the BHS using the top quartile allows for a population-specific distribution of the BHS which classifies those exposed to more extreme levels of system activity relative to the rest of the population and thus potentially at greater risk of developing disease. Moreover, prior research has shown that the latter method predicts health outcomes as well as other algorithms for scoring risk, including averaging the computed z-scores for each measure or using clinical cut-offs to define the 'at risk' group (Seeman et al., 1997, 2008; Beckie, 2012).

2.3. Longitudinal score

As the biomarkers were measured in Tromsø6 and 7, we constructed a longitudinal score that used the dichotomous risk indicator for each biomarker for both time points (Graves and Nowakowski, 2017). Each biomarker was given a score between 0 and 3 as follows. A participant's score was 0 if they had a value of 0 (not at-risk) for the dichotomized biomarker at both time points. The score was 1 if the value of the dichotomized biomarker decreased from 1 (at-risk) to 0 (not at-risk) between time points. The score was 2 if the value of the dichotomized biomarker increased from 0 (not at-risk) to 1 (at-risk) between time points. Finally, the score was 3 if the value of the dichotomized biomarker was 1 for both time points. For each biomarker, four groups were then created: stable low; decreasing; increasing; stable high.

We assumed that an increase in score between the two waves indicated an increase in biological risk, a decrease representing a lowering of risk. This is consistent with two previous studies that show decreasing AL score over time is associated with a decreased risk in mortality among adults over 55 years old (Karlamangla et al., 2006; Hwang et al., 2014). We also therefore assumed that being at risk in both waves was associated with the highest biological risk, while being not at risk at both waves represented the lowest biological risk.

The scores for each of the 10 biomarkers were then summed and the longitudinal score ranged theoretically from 0 to 30, with 0 indicating being in the not at-risk group at both waves for all the 10 biomarkers and 30 indicating being at-risk for all biomarkers at both waves.

2.4. Education

Educational attainment was used as a proxy for social position (Khalatbari-Soltani et al., 2022). The highest attained level of education was self-reported in a questionnaire and classified as follows: primary/ secondary school; technical/ vocational school; High School Diploma; tertiary education, short (college/university less than 4years); tertiary education, long (college/university 4years or more). To ensure that our exposure measure occurred prior to the BHS measurement, education measured in the fourth wave in 1994/95 (Tromsø4) was used in priority, and missing values (n = 1495, 18 %) were completed using education from Tromsø6.

2.5. Covariates

We included covariates collected in Tromsø6. We considered sex and age as potential confounders and lifestyle, body mass index (BMI) and medication as intermediate variables.

We used age at inclusion as a continuous variable. Smoking (daily smoker; former smoker; non-smoker), physical activity (never; less than once a week; once a week; 2–3 times a week; approximately every day) and alcohol consumption (non-drinker; monthly or less frequently; 2–4 times a month; 2–3 times a week; 4+ times a week) were self-reported and used as originally coded in the study. BMI was calculated as weight (in kilogramme)/height^2 (in metre), with weight and height measured during the physical examination. Use of antihypertensive treatment, lipid-lowering drugs and treatments for diabetes was self-reported (currently; previously; never).

2.6. Statistical analysis

Data analyses were performed with R (version 4.1.3). We used the 'ggforestplot' package to build the graphs.

2.6.1. Descriptive analyses

Descriptive characteristics were reported with means (SD) for continuous variables and proportions for categorical variables.

Baseline characteristics of the population were compared by educational level. Chi-squared test or Fisher's exact test for categorical variables, and T-test or Wilcoxon rank test for continuous variables were used to estimate bivariate associations with education.

2.6.2. Multivariable analyses

We conducted multivariable linear regressions to investigate the

association between education and BHS at each wave (Tromsø6 and 7) and longitudinally. We reported regression coefficients (betas, βs) and 95 % confidence interval (95 % CI). The first model was crude (model 1), then we further adjusted for age and sex (model 2), alcohol and tobacco consumption as well as physical activity (model 3), BMI (model 4) and finally for medication (model 5). In the present analysis, we considered BMI as a proxy for the outcome of previous health behaviours, including dietary patterns, physical activity, and overall nutrition. As such, we treated BMI similarly to the health behaviours/ lifestyle factors included in the analyses i.e. as a potential mediator.

In order to investigate the social pattern of each biomarker constitutive of the BHS, we standardized each biomarker (mean-centred and scaled to unit variance) and we conducted multivariable linear regressions between education and individual biomarker z-scores (same five models as described above).

2.6.3. Sensitivity analyses

We conducted different sets of sensitivity analyses to ensure the robustness of the results. Instead of the classic 25 %-threshold (quartile), we ran our analyses between education and BHS using i) a cut-off at 30 % to build the BHS in Tromsø6 and 7, ii) clinical thresholds for each biomarker to build the BHS in Tromsø6 and 7, and iii) Tromsø6 (sex and age-specific) thresholds to build the BHS in Tromsø7. We also conducted change scores analysis, modelling BHS at Tromsø7 while adjusting for baseline BHS (BHS at Tromsø6) in all models.

3. Results

3.1. Characteristics of the study population

Of the 8903 participants with data from both Tromsø6 and 7, we excluded 328 participants with missing data for at least one of the ten biomarkers and we further excluded 458 participants with missing data for covariates, leading to a study population of 8117 complete cases (Fig. 1).

Included participants were more often men (47 % vs 38 %, $p = 2.4 *10^{-6}$) and younger (55.4 vs 60.1 years old, $p < 10^{-16}$) compared to excluded participants (n = 786). Table 1 presents the distribution of selected characteristics of the included Tromsø Study participants. Women represented 53 % of the sample and mean (SD) age in Tromsø6 was 55 (11) years old (age range: [32–87] years in Tromsø6, [40–95] years in Tromsø7). Regarding education, 20 % of the sample had a higher tertiary education and 25 % declared a primary/secondary school level. In terms of health behaviours, 18 % were active smokers,

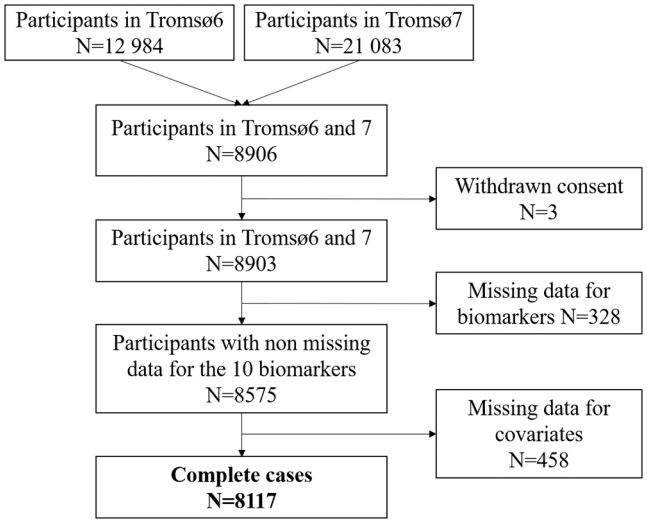

Fig. 1. Flowchart of participants. The Tromsø Study 2007–2016.

around 25 % drank alcohol more than once a week, and 20 % exercised every day. In Tromsø6, participants taking antihypertensive drugs, lipid-lowering drugs and antidiabetic drugs represented respectively 18 %, 12 % and 3 %.

Mean (SD) BHS in Tromsø6 and 7 were very similar (2.34 (1.92) vs 2.35 (1.89)) and mean (SD) longitudinal BHS was 7 (5.1). Looking at individual biomarkers, participants in this sample had values within the healthy range defined by the clinical thresholds. Detailed information regarding distributions of BHS are available in supplementary Table A1.

3.2. Education and BHS in Tromsø6 and 7

Linear regression models carried out on BHS at each wave revealed a strong educational gradient, the lower the educational attainment, the higher the BHS. In Tromsø6, participants with a primary/secondary school level were more likely to have a higher BHS compared to those with more than 4 years of university (Model 1, β = 0.84 [95 % CI=0.72;0.97]). Controlling for age and sex only marginally impacted this association (Model 2, β = 0.76 [95 % CI=0.63;0.89]). Additional adjustments for health behaviours weakened this association (Model 3, β = 0.50 [95 % CI=0.37;0.64]) and, subsequently, for BMI, narrowed further this gradient (Model 4, β = 0.31 [95 % CI=0.18;0.44]). In the fully-adjusted model (Model 5), participants with the lowest educational level still had a 0.30-point [95 % CI= 0.18;0.43] higher BHS compared to those with the highest educational level. A similar pattern was observed in Tromsø7: participants with a primary/secondary school level had a higher BHS compared to those with more than 4 years of university (Model 1, β = 0.70 [95 % CI=0.58;0.82]) and this association was not entirely explained by health behaviours, BMI and medication (Model 5, β = 0.30 [95 % CI=0.17;0.42]) (Fig. 2).

Participants with a technical school level, high school diploma or college/university less than 4 years also presented higher BHS compared to participants with the highest educational level. Sequential adjustments narrowed the association with the BHS, however the association persisted in the fully-adjusted model (Model 5) for technical school and high school diploma. Trends were similar in both Tromsø6 and 7.

3.3. Educational patterning of individual biomarkers

We examined the relationship between educational attainment and each z-score of biomarkers composing the BHS (Fig. 3 and supplementary Table A.2). In Model 2 adjusted for sex and age, participants with a primary/secondary school level were at greater risk of having higher levels of SBP, pulse rate, CRP, total and LDL-cholesterol, triglycerides and Hba1c and lower levels of HDL-cholesterol compared to those with more than 4 years of university in Tromsø6. In Tromsø7, participants with a primary/secondary school level were at greater risk of having higher levels of SBP, DBP, pulse rate, triglycerides and Hba1c and lower levels of HDL-cholesterol (Fig. 3, model 2).

Adjustments for health behaviours, BMI and medication did explain some associations, for example for glycated haemoglobin or HDL-cholesterol. However, the educational gradient strongly persisted for SBP in both waves. Compared to those with more than 4 years of university, participants with a primary/secondary school level had a 0.19-point [0.13;0.25] and a 0.23-point [0.17;0.30] higher z-score of SBP in Tromsø6 and 7 respectively (Fig. 3, model 5). The relationship with education also remained for total cholesterol in Tromsø6, DBP in Tromsø7 as well as for pulse and triglycerides at both waves. Detailed results for all the five models are available in Supplementary material (Table A.2).

3.4. Education and longitudinal BHS

The longitudinal BHS was obtained by summing individual longitudinal biomarker-specific distributions and ranged from 0 to 28 with a mean (SD) value of 7 (5.1). Around 9 % of participants had a

Table 1
Demographic and biological characteristics by study wave and categories of educational attainment. The Tromsø Study 2007–2016.

Characteristics	Total N = 8117[1]	College/ University 4 + years N = 1592[1]	College/ University less than 4 years N = 1478[1]	High School diploma N = 749[1]	Technical school N = 2250[1]	Primary/secondary school N = 2048[1]	p-value[2]
Biomarkers at Tromsø6							
Biological Health score	2.34 (1.92)	1.87 (1.78)	2.12 (1.83)	2.35 (1.99)	2.48 (1.92)	2.72 (1.95)	<0.001
Systolic blood pressure (mmHg)	133.35 (21.56)	128.46 (20.36)	130.85 (20.87)	128.21 (20.30)	134.34 (21.09)	139.76 (22.18)	<0.001
Diastolic blood pressure (mmHg)	77.64 (10.50)	76.87 (10.75)	77.16 (10.40)	76.98 (10.69)	78.16 (10.24)	78.25 (10.51)	<0.001
Pulse rate (bpm)	64.30 (9.90)	62.77 (9.73)	63.34 (9.58)	64.29 (9.86)	65.05 (10.01)	65.36 (9.95)	<0.001
Serum total cholesterol (mmol/L)	5.62 (1.07)	5.44 (1.01)	5.47 (1.04)	5.53 (1.04)	5.71 (1.07)	5.80 (1.09)	<0.001
Serum HDL-cholesterol (mmol/L)	1.51 (0.42)	1.58 (0.44)	1.51 (0.43)	1.48 (0.39)	1.49 (0.42)	1.51 (0.42)	<0.001
Serum LDL- cholesterol (mmol/L)	3.57 (0.93)	3.38 (0.89)	3.45 (0.92)	3.51 (0.91)	3.66 (0.92)	3.72 (0.97)	<0.001
Serum triglycerides (mmol/L)	1.51 (0.90)	1.37 (0.80)	1.46 (0.87)	1.48 (0.88)	1.57 (0.96)	1.58 (0.91)	<0.001
Serum glucose (mmol/L)	5.17 (1.07)	5.09 (1.04)	5.15 (1.05)	5.10 (0.96)	5.18 (1.03)	5.28 (1.18)	<0.001
HbA1c (%)	5.58 (0.58)	5.47 (0.50)	5.55 (0.56)	5.50 (0.54)	5.61 (0.57)	5.71 (0.64)	<0.001
Serum CRP sensitive (mg/L)	2.27 (4.22)	1.62 (2.58)	2.27 (4.32)	1.99 (2.85)	2.46 (4.27)	2.66 (5.32)	<0.001
Biomarkers at Tromsø7							
Biological Health score	2.35 (1.89)	1.96 (1.80)	2.15 (1.84)	2.41 (1.92)	2.46 (1.90)	2.66 (1.90)	<0.001
Systolic blood pressure (mmHg)	133.47 (20.72)	128.48 (19.66)	131.33 (20.23)	128.96 (19.51)	134.46 (20.18)	139.45 (21.28)	<0.001
Diastolic blood pressure (mmHg)	75.47 (10.00)	74.67 (9.93)	75.23 (9.73)	75.55 (10.47)	75.82 (9.87)	75.86 (10.17)	0.002
Pulse rate (bpm)	66.96 (11.26)	65.80 (10.66)	66.31 (11.19)	67.18 (10.85)	67.59 (11.43)	67.57 (11.65)	<0.001
Serum total cholesterol (mmol/L)	5.48 (1.07)	5.49 (1.02)	5.39 (1.06)	5.54 (1.07)	5.49 (1.08)	5.49 (1.11)	0.033
Serum HDL- cholesterol (mmol/L)	1.61 (0.49)	1.69 (0.50)	1.61 (0.50)	1.58 (0.45)	1.58 (0.49)	1.59 (0.48)	<0.001
Serum LDL- cholesterol (mmol/L)	3.57 (0.99)	3.54 (0.93)	3.49 (0.97)	3.65 (1.00)	3.59 (0.99)	3.58 (1.03)	0.014
Serum triglycerides (mmol/L)	1.49 (0.83)	1.37 (0.78)	1.44 (0.80)	1.51 (0.97)	1.53 (0.83)	1.55 (0.84)	<0.001
Serum glucose (mmol/L)	5.53 (1.40)	5.45 (1.34)	5.51 (1.36)	5.44 (1.26)	5.56 (1.48)	5.61 (1.43)	<0.001
HbA1c (%)	5.76 (0.60)	5.64 (0.49)	5.72 (0.58)	5.68 (0.56)	5.78 (0.65)	5.87 (0.64)	<0.001
Serum CRP sensitive (mg/L)	2.12 (5.65)	1.81 (6.87)	2.03 (5.20)	2.01 (5.94)	2.09 (4.18)	2.52 (6.15)	<0.001
Longitudinal BHS	7.04 (5.08)	5.78 (4.86)	6.43 (4.90)	7.16 (5.29)	7.41 (5.07)	8.02 (5.08)	<0.001
Covariates (Tromsø6)							
Sex							<0.001
Male	3829 (47 %)	725 (46 %)	780 (53 %)	306 (41 %)	1133 (50 %)	885 (43 %)	
Female	4288 (53 %)	867 (54 %)	698 (47 %)	443 (59 %)	1117 (50 %)	1163 (57 %)	
Age	55.39 (11.06)	52.24 (10.55)	53.72 (10.78)	50.01 (9.86)	56.05 (10.74)	60.28 (10.36)	<0.001
Do you smoke cigarettes daily?							<0.001
Yes now	1445 (18 %)	140 (8.8 %)	196 (13 %)	145 (19 %)	464 (21 %)	500 (24 %)	
Yes previously	3512 (43 %)	587 (37 %)	607 (41 %)	308 (41 %)	1036 (46 %)	974 (48 %)	
Never	3160 (39 %)	865 (54 %)	675 (46 %)	296 (40 %)	750 (33 %)	574 (28 %)	
How often do you usually drink alcohol?							<0.001
Never	641 (7.9 %)	75 (4.7 %)	91 (6.2 %)	42 (5.6 %)	162 (7.2 %)	271 (13 %)	
Monthly or less frequently	2175 (27 %)	282 (18 %)	319 (22 %)	184 (25 %)	635 (28 %)	755 (37 %)	
2–4 times a month	3324 (41 %)	566 (36 %)	648 (44 %)	360 (48 %)	988 (44 %)	762 (37 %)	
2–3 times a week	1544 (19 %)	490 (31 %)	325 (22 %)	141 (19 %)	378 (17 %)	210 (10 %)	
4 + times a week	433 (5.3 %)	179 (11 %)	95 (6.4 %)	22 (2.9 %)	87 (3.9 %)	50 (2.4 %)	
How often do you exercise?							<0.001
Never	317 (3.9 %)	28 (1.8 %)	25 (1.7 %)	26 (3.5 %)	87 (3.9 %)	151 (7.4 %)	
< 1/week	1247 (15 %)	155 (9.7 %)	224 (15 %)	103 (14 %)	400 (18 %)	365 (18 %)	
1/week	1709 (21 %)	332 (21 %)	314 (21 %)	160 (21 %)	505 (22 %)	398 (19 %)	
2–3 times/week	3259 (40 %)	709 (45 %)	614 (42 %)	317 (42 %)	873 (39 %)	746 (36 %)	
Approx. every day	1585 (20 %)	368 (23 %)	301 (20 %)	143 (19 %)	385 (17 %)	388 (19 %)	
Body mass index (kg/m2)	26.80 (4.12)	25.79 (3.84)	26.59 (4.03)	26.76 (4.19)	27.09 (4.05)	27.42 (4.30)	<0.001
Do you use blood pressure lowering drugs?							<0.001
Never	6493 (80 %)	1391 (87 %)	1219 (82 %)	662 (88 %)	1742 (77 %)	1479 (72 %)	
Currently	1486 (18 %)	171 (11 %)	240 (16 %)	78 (10 %)	463 (21 %)	534 (26 %)	
Previously	138 (1.7 %)	30 (1.9 %)	19 (1.3 %)	9 (1.2 %)	45 (2.0 %)	35 (1.7 %)	
Do you use cholesterol lowering drugs?							<0.001
Never	7055 (87 %)	1475 (93 %)	1307 (88 %)	705 (94 %)	1927 (86 %)	1641 (80 %)	
Currently	951 (12 %)	111 (7.0 %)	154 (10 %)	40 (5.3 %)	287 (13 %)	359 (18 %)	
Previously	111 (1.4 %)	6 (0.4 %)	17 (1.2 %)	4 (0.5 %)	36 (1.6 %)	48 (2.3 %)	
Do you use tablet for diabetes?							0.007
Never	7885 (97 %)	1565 (98 %)	1433 (97 %)	732 (98 %)	2186 (97 %)	1969 (96 %)	
Currently	210 (2.6 %)	27 (1.7 %)	39 (2.6 %)	15 (2.0 %)	60 (2.7 %)	69 (3.4 %)	
Previously	22 (0.3 %)	0 (0 %)	6 (0.4 %)	2 (0.3 %)	4 (0.2 %)	10 (0.5 %)	

[1] Mean (SD); n (%)
[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test.
BHS: Biological Health Score; CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

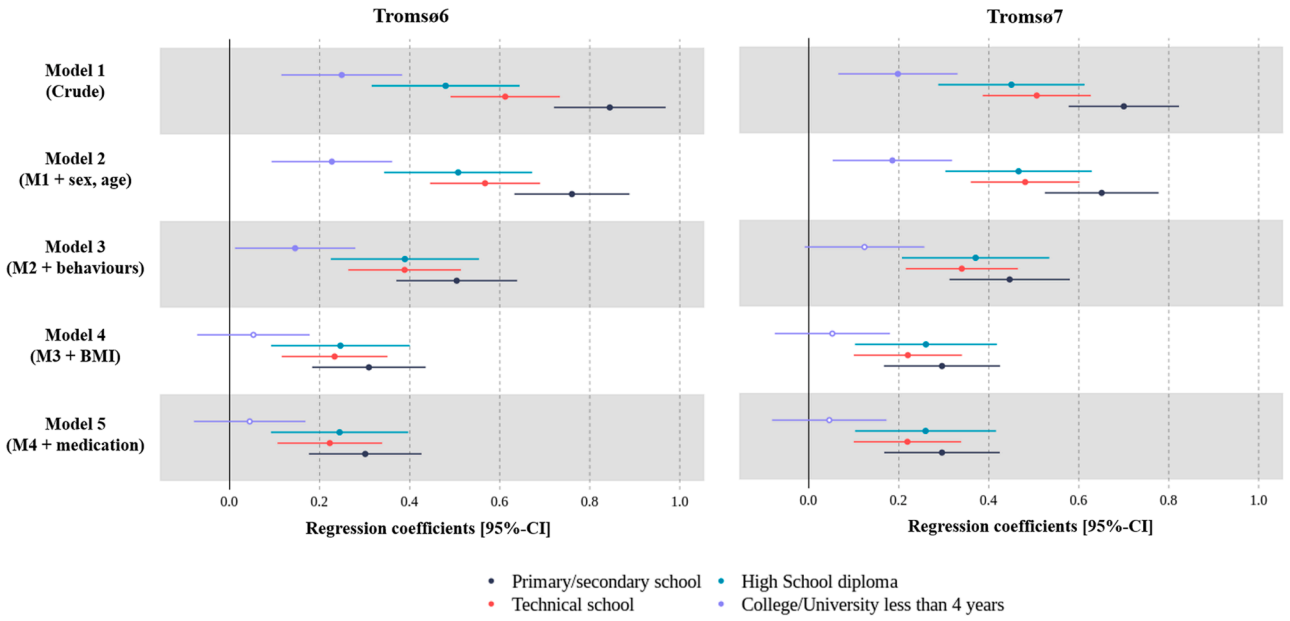

Fig. 2. Linear association between education and BHS by wave. The Tromsø Study 2007–2016.
Reference category: College/university 4 y or more.
Non-significant test of the null hypothesis that a coefficient equals zero are displayed as hollow points.
Model 1 is unadjusted. Model 2 is adjusted for sex and age. Model 3 is further adjusted for health behaviours (smoking, alcohol consumption, physical activity). Model 4 is further adjusted for body mass index and model 5 is further adjusted for medication uptake.

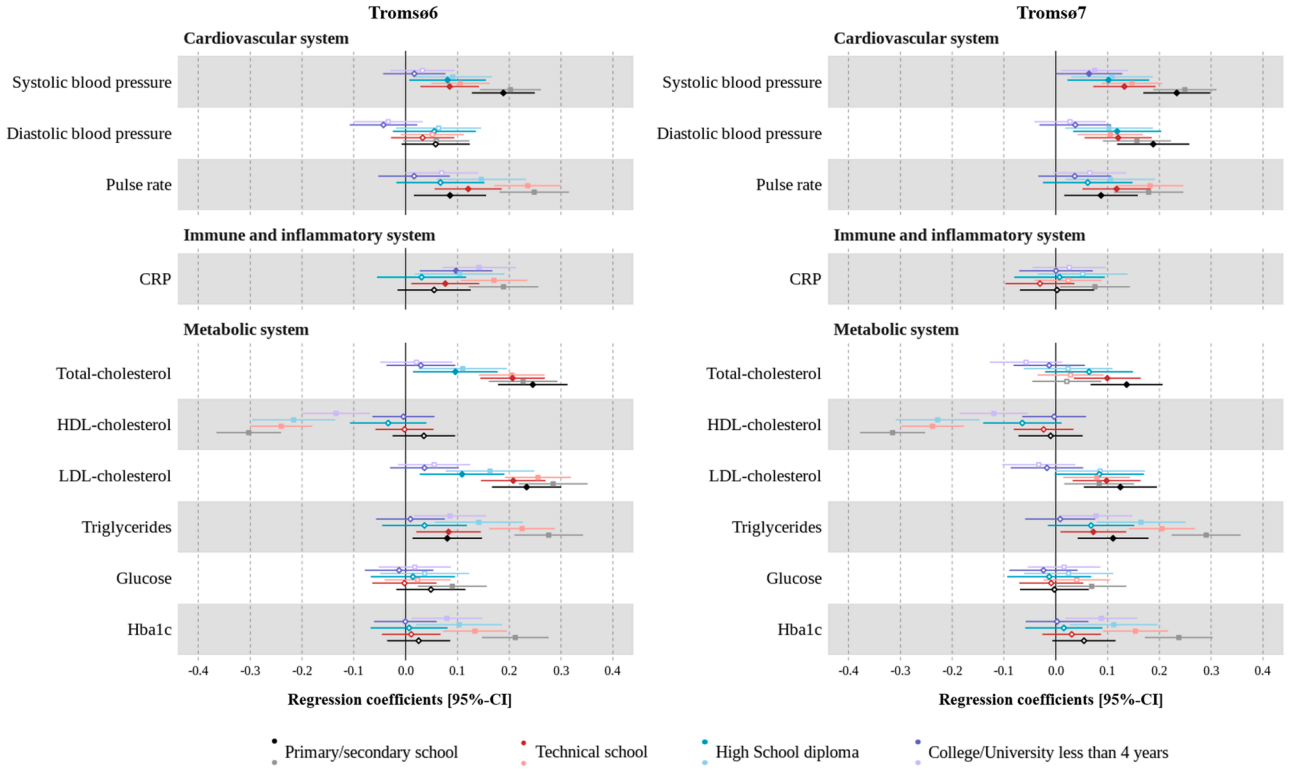

Fig. 3. Linear association between education and Z-scores of individual biomarkers by wave. The Tromsø Study 2007–2016.
Model 2 (in transparent) is adjusted for sex and age. Model 5 (in bold) is further adjusted for smoking, physical activity, alcohol consumption, body mass index and medication uptake.

longitudinal BHS equal to 0, which means that 9 % of the participants stayed in the 'not at risk' group for all the ten biomarkers across Tromsø6 and 7. In descriptive analyses, longitudinal BHS increased with decreasing educational attainment (supplementary Figure A1). Linear regression models (Fig. 4) revealed a strong educational gradient, with a higher longitudinal BHS observed among those with a lower educational attainment: participants with a primary/secondary school level had a 2.25-point [95 % CI= 1.92;2.57] higher longitudinal BHS compared to

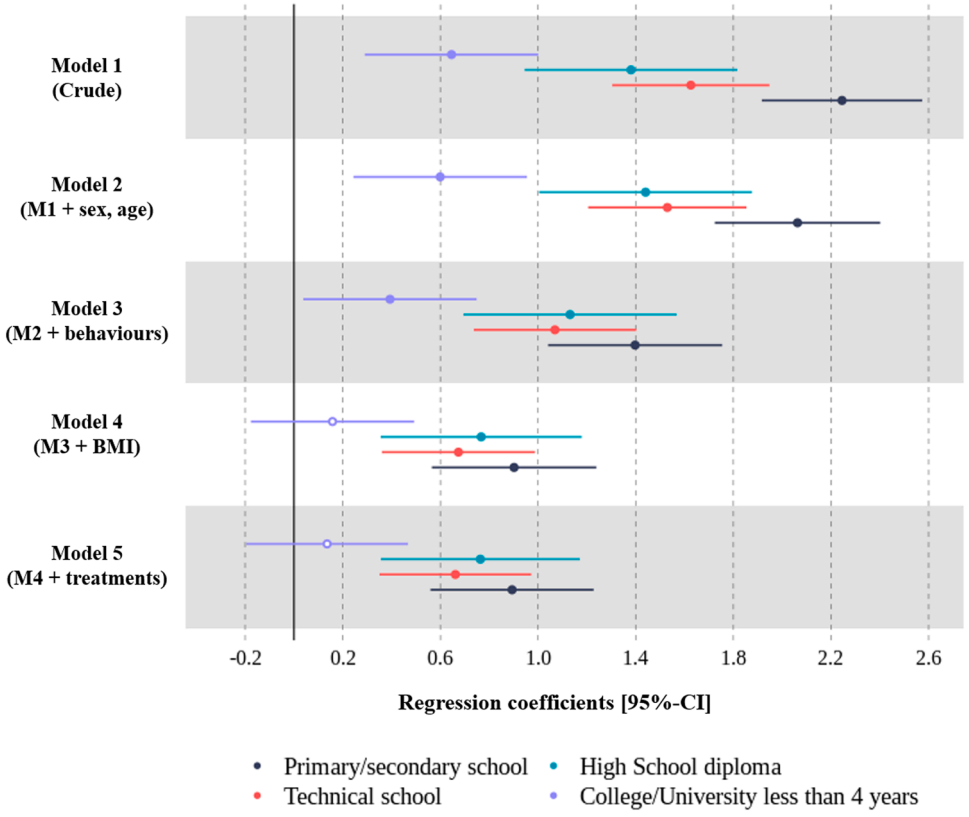

Fig. 4. Linear association between education and longitudinal BHS. The Tromsø Study 2007–2016.
Reference category: College/university 4y or more.
Model 1 is unadjusted. Model 2 is adjusted for sex and age. Model 3 is further adjusted for health behaviours (smoking, alcohol consumption, physical activity). Model 4 is further adjusted for body mass index and model 5 is further adjusted for medication uptake.

those with more than 4 years of university (Model 1). Controlling for age and sex only marginally impacted this association (Model 2, $\beta = 2.06$ [95 % CI=1.72;2.40]). Additional adjustments for health behaviours (Model 3, $\beta = 1.40$ [95 % CI=1.04;1.75]) weakened this association and, subsequently, for BMI, narrowed further this gradient (Model 4, $\beta = 0.90$ [95 % CI=0.56;1.24]) but did not completely explain this association. In the fully-adjusted model (Model 5), participants with the lowest educational level still had a 0.89-point [95 % CI= 0.56;1.23] higher longitudinal BHS compared to those with the highest educational level.

3.5. *Educational patterning of longitudinal biomarker-specific distributions*

The longitudinal biomarker-specific distributions are presented in supplementary Figure A2. Hba1c and HDL-cholesterol were biomarkers with the highest proportions of stable individuals ("stable low" / "stable high") whereas glucose, systolic and diastolic blood pressure were biomarkers with the highest proportions of participants with "increasing"/ "decreasing" scores.

The longitudinal biomarker-specific distributions across levels of education is presented in Fig. 5. There is a clear trend of a decreasing proportion of people in the "stable low" group with decreasing educational levels that was visible for the majority of biomarkers, except for glucose. Conversely, the proportion of people in the "stable high" group tended to increase with decreasing educational levels, and this is especially clear for HDL-cholesterol, triglycerides, hba1c and CRP. The proportion of people whose scores increased or decreased between the two time points also tended to increase with decreasing educational levels.

3.6. *Sensitivity analyses*

Sensitivity analyses were conducted using different thresholds to build wave-specific and longitudinal BHS and are presented in Supplementary Material. Using a 30 %-threshold based on sex- and age-specific distributions (Table A.3), clinical thresholds for each biomarker (Table A.4) or Tromsø6 sex- and age-specific thresholds for each biomarker at Tromsø7 (Table A.5) did not substantially modify the results. Specifically, using a 30 %-threshold or clinical cut-offs, we observed a more visible educational gradient with clearer differences between participants with High School Diploma and those with a technical school degree. In addition, in models built using clinical cut-offs, we observed a stronger role of sex and age (larger attenuation between Model 1 and Model 2) and slightly smaller effect sizes compared to the main analysis – especially for BHS at Tromsø6 and longitudinal BHS –, whereas in models built using a 30 %-threshold, effect sizes were slightly bigger compared to the main analysis – especially for BHS at Tromsø7 and longitudinal BHS. We also conducted complementary change scores analysis, modelling BHS at Tromsø7 while adjusting for BHS at Tromsø6 in all the 5 models (Table A.6). In these models, we observed similar trends of a higher risk of elevated BHS at Tromsø7 among participants with lower education although the distinction between tertiary short and long education, and between High School Diploma and technical school levels were less visible. In addition, effect sizes were smaller, as was the contribution of confounding factors and intermediate variables.

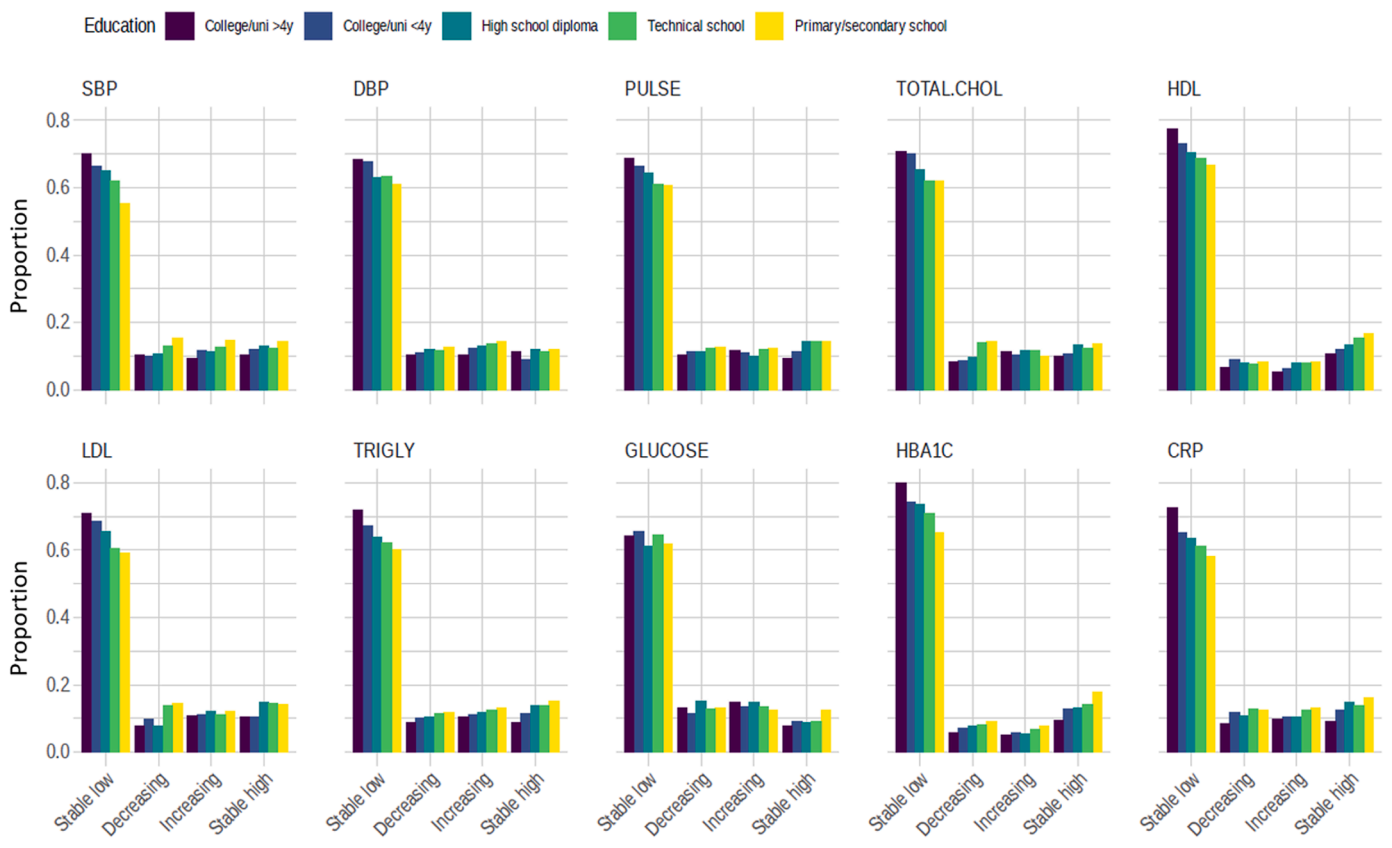

Fig. 5. Distribution of the biomarker-specific longitudinal score by educational attainment. The Tromsø Study 2007–2016. All p-values for differences in distributions are <0.001.

4. Discussion

4.1. Main findings

We found a persistent educational gradient in a composite biological health score at two distinct time points but also over time. People with lower educational attainment were at greater biological risk at both Tromsø6 and 7. They also presented higher longitudinal BHS compared to people with higher education, meaning that their biological health had deteriorated to a greater extent over time. We found that certain biomarkers related to the cardiovascular system and the metabolic system were strongly socially distributed, independent of confounders. This relationship persisted after adjusting for health behaviours and BMI.

4.2. Social gradient in BHS

The relationship between education, as a marker for socioeconomic position, and BHS in Tromsø6 and 7 that we identified in the Norwegian context is consistent with findings from previous studies that also used education (Karimi et al., 2019; Chadeau-Hyam et al., 2020) or other markers of the social environment (Barboza Solís et al., 2015, 2016). However, a striking result of the present work is that individuals with lower educational attainment not only start out with a higher BHS at baseline (Tromsø6) but also see their BHS increase over time, resulting in a higher longitudinal BHS. This change in wear-and-tear over time in relation to socioeconomic position has rarely been investigated in the literature and conclusions remain unclear, some papers highlighting a global (or restricted to subgroups) moderating influence of socioeconomic position on changes in AL over time (Merkin et al., 2014; Upchurch et al., 2015; Graves and Nowakowski, 2017; van Deurzen and Vanhoutte, 2019) or no association (Chyu and Upchurch, 2018; Merkin et al., 2020; Richards et al., 2023). In the present study, we found that participants with lower educational attainment had a higher longitudinal BHS, which suggests that their biological health has deteriorated to a greater extent over time. Previous works reported that, compared with participants whose AL score decreased over time, participants whose AL score increased fast had a higher risk of mortality, adjusted for age and sex (Karlamangla et al., 2006; Hwang et al., 2014). The relationship between changes in biological scores of wear-and-tear and health deserves to be studied in more depth. This may be of particular importance from a public health perspective, especially given the accumulation of differences in BHS by education level over time, and highlights the need to better understand the social-to-biological processes linking education and biological health.

In order to understand the potential mechanisms that may affect the relation between education and the BHS, we sequentially adjusted for intermediate variables related to lifestyle and behaviours. The relationship between education and biological health was attenuated after adjusting for health behaviours, BMI and medication use and the observed changes to effect size after adjustments are consistent with previous findings. Our results are also consistent with the documented association linking the social environment and BMI (McLaren, 2007). In our work, BMI appeared as a particularly important potential mediator of the association between education and biological risk in Norwegian adults and this underlines the powerful role of BMI in the prevention of social inequalities in health. It is however noteworthy that the association between lower educational attainment and higher BHS remained after adjusting for all covariates, highlighting that other mechanisms are involved in the way education exerts its effect on biological health. The relationship between education and health is complex and three main underlying pathways have been discussed in the literature, which may operate simultaneously. The behavioural pathway suggests that individuals with higher education may present a higher level of health

literacy, but also increased personal control in their life or at work (Hayward et al., 2015), which in turn can lead to the adoption of healthy behaviours. The material pathway emphasizes that highly educated adults are more likely to have access to favourable material conditions and assets through better employment and income conditions. The psychosocial pathway focuses on how education mitigates the direct and indirect effects of social and psychological stressors (Bartley, 2016). We assume the crucial importance of considering psychosocial factors when investigating how social inequalities in health are constructed, and this is still lacking. This dimension of the social environment deserves specific attention as a multidimensional set of health determinants and needs to be conceptualized in the global framework to reflect the specificity and complexity of such variables. Moreover, these individuals with lower educational attainment also seem to have more volatile biological profiles in the Tromsø Study, being more frequently identified in the 'increasing' and 'decreasing' groups of the biomarker-specific longitudinal scores (Fig. 5).

4.3. Education and individual biomarkers

We also investigated the social patterning of biomarkers composing the BHS individually. We found that the association with education was the strongest in two major systems: the cardiovascular and the metabolic systems, and more specifically by two biomarkers: systolic blood pressure (both Tromsø6 and 7) and total cholesterol level (stronger in Tromsø6), for which the educational gradient remained steep after accounting for confounders and potential intermediate variables. One possible explanation for seeing such a strong association between education and blood pressure might be related to the lack of accounting for psychosocial variables in our models, as blood pressure is a biomarker which is strongly influenced by the ortho- and para-sympathetic systems, two systems that are closely related to stress. Regarding cholesterol, the persistent association with education seems to be mostly driven by LDL-cholesterol; yet a specific adjustment on dietary profiles is lacking in our models.

4.4. Strengths and limitations

One major strength of this work is the high-quality dataset with large sample size of adults aged 32–87 years, broad range of biomarkers, few missing data and available data on follow-up that allow us to conduct longitudinal analyses of the relationship between education and BHS. The ability to study the BHS at two time points allowed us to study the evolution of this score with respect to education and its impact on health, which is a strong originality of this work. Moreover, few studies have investigated the social-to-biological transition in Norway compared to other countries and the Tromsø Study allows us to do so. Second, we performed several sensitivity analyses that assessed the robustness of our results. However, some limitations need to be mentioned. First, we used a composite BHS to assess biological risk at specific time points and over time as a proxy for physiological wear-and-tear. This method focuses on a pre-clinical state of individuals, which means that we are interested in those at the top of the biomarker-specific distributions before the onset of clinical symptoms. Biomarkers are used as proxies for global biological health and not as clinical indicators. Nevertheless, the sensitivity analyses conducted using clinical thresholds to build the BHS did not modify the main results. Regarding the construction of the BHS, we used the count-based method, which is the most common approach in published studies and has been shown to perform well relative to more complicated scoring systems (Li et al., 2019; McCrory et al., 2023; McLoughlin et al., 2020; Seplaki et al., 2005). However, we cannot exclude that this may have affected our results. Regarding the construction of the longitudinal score, it may be debatable that decreasing risk between waves indicates less risk, nevertheless, we considered that not being at risk in either wave should theoretically have less cumulative biological impact. Second, we used education as a proxy for social position. However, education captures only part of the multiple and complex dimensions of the social environment that may be embodied over the life course. There is a need to examine other measures of socio-economic position both at the individual and aggregate level that would provide additional insight into embodiment processes. Third, we included in our analyses various confounders and potential mediators of the relationship between education and biological health. However, we did not include factors related to dietary patterns, nor potential mediators related to the material or psychosocial pathways. Also, we adjusted our models for longitudinal BHS using covariates at Tromsø6 and did not account for changes in the intermediate variables such as lifestyle factors. Moreover, we included antihypertensive, antidiabetic and lipid-lowering drugs as intermediate variables to approximate the effect of treatment received within the healthcare system. We acknowledge that this approach is a proxy capturing possible effects due to the healthcare system, and unmeasured factors may still play a role. In addition, there might be some residual confounding. Fourth, as with all observational studies, bias introduced through sample selection may be an issue. The sample selection of Tromsø Study participants may differ from the general population of people residing in the catchment area, and loss-to follow-up over time of people with certain characteristics may also play a role in biasing the sample used for analysis.

5. Conclusions

We identified a strong educational gradient in biological health, with higher BHS being observed among participants with lower education in both Tromsø6 and 7. In addition, the repeated measurements of biomarkers, which are rarely available, allowed us to compute a longitudinal BHS to study the association between education and biological health over time. This longitudinal analysis showed that participants with lower education presented higher longitudinal BHS compared to people with higher education, highlighting that their biological health has deteriorated to a greater extent over time. Our findings provide further evidence for the biological embodiment of the social environment, particularly with respect to dynamic aspects for which little evidence exists. This suggests that education has a lasting impact on biology into adulthood through various potential mechanisms which deserve to be further investigated. In particular, counterfactual mediation analyses assessing direct, indirect and total effects are needed to evaluate the contribution of potential mediators (such as behaviours) to the educational gradient in BHS in this Norwegian population.

CRediT authorship contribution statement

LN, RC, CD and MKI conceived the study. LN did the data curation, performed the statistical analyses and drafted the original manuscript. RC, CD and MKI provided insights into the results interpretation and critically revised the manuscript. TW, SG, MCH, DV, AUP, EHF, TMS critically revised the manuscript. MKI and CD supervised the work.

Data sharing statement

Access to sensitive and personal data such as those of the Tromsø Study is restricted. Data can be made available, upon request, to researchers who have prior obtained the approval of the Data- and Publication Committee (DPC) of the Tromsø Study. Information for applicants is available at: https://uit.no/research/tromsostudy.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. MCH holds shares in the O-SMOSE company and has no conflict of interest to disclose. Consulting activities conducted by the company are independent of the present work.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2023.106670.

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