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BMJ Open Biological embodiment of educational attainment and future risk of breast cancer: findings from a French prospective cohort

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ABSTRACT

Background Women with higher educational attainment have a higher risk of developing breast cancer (BC).

Despite the acknowledged impact of reproductive and lifestyle factors, some excess risks remain unexplained. Many studies support the hypothesis that education has a distinctive effect on physiological processes associated with health, independently of known risk factors.

Objectives In this study, we aimed to determine whether the biological embodiment of education could be part of the observed social inequalities in BC risk. We focused on biomarkers from several physiological systems examined individually, and jointly through a biological health score (BHS).

Design Prospective cohort study.

Setting This study, based on a subsample of the French E3N cohort, included women with biological data from four nested case-control studies.

Participants The study included 3048 postmenopausal women (17% BC).

Main outcome measures We first evaluated the association between educational attainment and each biomarker, separately (N=11) and by combining them into a BHS, indicative of an augmented biological health hazard when elevated. Finally, we explored the relationships between the socially patterned biomarkers and BHS, and risk of incident BC.

Results Women with higher educational attainment exhibited a lower BHS in comparison to those with lower educational attainment ($\beta_{\text{high education}} = -0.21$ (95% CI -0.42 ; 0.01), model 2). Specific biomarkers associated with the cardiovascular (systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides (TG), high-density lipoprotein (HDL)), inflammatory (C reactive protein (CRP)) and hormonal systems (sex hormone-binding globulin (SHBG) and oestradiol) were found socially distributed (OR_{CRP-high} = 0.70 (95% CI 0.54; 0.91), OR_{TG-high} = 0.79 (95% CI 0.61; 1.04), OR_{DBP-high} = 0.69 (95% CI 0.53; 0.90), OR_{SBP-high} = 0.57 (95% CI 0.44; 0.74), OR_{HDL-high} = 0.79 (95% CI 0.60; 1.03), (OR_{SHBG-high} = 0.67 (95% CI 0.52; 0.88), OR_{oestradiol-high} = 1.34 (95% CI 1.00; 1.79); model 1). Associations persisted after adjustment for cofounders and a large set of potential mediators for two of the investigated cardiovascular markers (OR_{DBP-high} = 0.75 (95% CI 0.57; 1.00), OR_{SBP-high} = 0.61 (95% CI 0.46; 0.81); model 2). No

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This work was conducted on a subset of a large prospective cohort of French women, with a wide array of biomarkers and potential mediating factors.
- ⇒ The prospective design ensured that social, behavioural and reproductive exposures preceded biological measurements.
- ⇒ The prospective design limited, both recall and reverse causation biases.
- ⇒ The average educational level of the cohort was rather high in comparison to the general population, with less variability in educational attainment.
- ⇒ Selection bias may have occurred because measurements of biomarkers were made within several nested case-control studies with specific objectives and inclusion criteria, even after adjustment for case-control studies of the participants.

associations were found between the socially stratified biomarkers and BHS with risk of BC.

Conclusion Educational attainment has a direct impact on biological processes suggesting that the biological embodiment of the social environment could be a potential pathway that mediates the association between educational attainment and health. Further studies are needed to specifically investigate the relationships between socially stratified biomarkers and BC risk.

INTRODUCTION

Numerous studies have reported social inequalities in the incidence of breast cancer (BC), revealing that women with more advantaged socioeconomic positions (SEPs), mainly assessed by education, are at higher risk of developing BC^{1 2} compared with women with more disadvantaged SEP.

Although these social inequalities have been largely attributed to aetiological factors such as health behaviours and reproductive factors, a portion of the variation remains



unexplained,³⁻⁶ as previously reported in a study on the French E3N cohort which encompasses one of the largest sets of cofounders and potential mediators.⁷ According to that study, adjusting for health behaviours, anthropometric characteristics and BC screening had little effect on the association between educational attainment and BC development. However, accounting for a set of reproductive factors, including age at first childbirth, significantly weakened this association. Nonetheless, the effect of educational attainment on the risk of BC was not fully explained even after considering this large set of potential mediators.

These findings suggest that some unaccounted-for factors could be involved in the relationship between educational attainment and BC. Beyond the role of identified mediating factors, the link between education and BC risk may be partly due to biological modifications associated with education, which remain to be elucidated and better understood. A growing number of studies support the hypothesis that SEP may have an effect on different physiological processes^{8,9} throughout the life course, not entirely explained by known risk factors. They support evidence that social environment can be embodied¹⁰ through alternative pathways, particularly through exposures to chronic psychosocial stress. Numerous social experiences including adversities and discriminations elicit recurring adaptations within the human organism, a phenomenon also known as allostasis. These ongoing adaptive responses give rise to lasting physiological consequences, collectively known as 'allostatic load' (AL).¹¹⁻¹⁴ AL is often quantified by evaluating the levels of biomarkers that originate from physiological systems that are primarily and secondarily activated by the neuroendocrine system.^{13,14} Recently, a Biological Health Score (BHS) similar to AL has been developed, as it is better suited for measurement obtained in an epidemiological setting. This allows the inclusion of new biological systems into the score, such as liver or kidney systems.¹⁵ Several studies¹⁴⁻¹⁶ have shown that disadvantaged SEP is associated with higher AL and BHS.

The biological embodiment of SEP can also be explored by assessing the association between each specific biological system or individual biomarker and SEP. For instance, an association has been identified between disadvantaged SEP, mainly assessed through education, and elevated levels of C reactive protein (CRP), a systemic marker of inflammation, even after adjusting for potential mediators and confounding variables such as health behaviours or the body mass index (BMI).¹⁷⁻²² Research has also highlighted inverse relationships between, education and cardiovascular²³⁻²⁵ or cardiometabolic profiles,^{26,27} with some studies delineating unique cholesterol profiles among the less socially advantaged.²⁸ Few studies have examined SEP in relation to sex hormones. Sex-specific studies revealed that disadvantaged SEP was associated with a higher level of testosterone in women,²⁹⁻³¹ although others failed to demonstrate any association.³² No association was observed between education and oestradiol,³¹

nor with childhood SEP.³² Elevated levels of sex hormone-binding globulin (SHBG), a hormone that transports sex hormones and regulates their access to target tissues, were also reported in advantaged socioeconomic groups independently of adjustment for potential mediators.^{32,33} All the evidence suggests that SEP can influence different biological systems, and ultimately overall biological functioning, by involving classic potential pathways such as behaviour but also psychosocial exposures. However, further investigation into the biological embedding of the social environment is warranted.

The fact that SEP can alter biological functioning is not without consequences for health. A high AL score is consistently linked to elevated morbidity and mortality across multiple studies,¹³ and a higher overall cancer risk,³⁴ even after adjustment for health behaviours. However, it is unclear if this association is also found for specific cancer sites, especially BC,^{35,36} as the literature remains limited. BC development has long been associated with a dysregulation of inflammatory, metabolic, and cardiovascular biomarkers.³⁷⁻⁴²

Indeed, an increased risk of BC has been reported in women with elevated CRP, as shown by two recent meta-analyses,^{37,38} as well as in women with hypertension or higher systolic blood pressure (SBP),^{41,42} and in women with high levels of oestradiol and/or testosterone and low levels of SHBG.⁴³⁻⁵⁰ By contrast, elevated levels of cholesterol, especially high-density lipoprotein (HDL) and triglycerides (TG), have been associated with decreased risk of BC.^{39,40}

To our knowledge, no studies have considered whether some of the long-term BC excess risk associated with education may be attributed to biological embodiment of SEP reflected by variations in BHS or individual biomarkers. By leveraging a subset of the French E3N cohort comprising women with data on social exposure, biological markers and BC diagnoses, this study aimed to (1) analyse the influence of educational attainment on the BHS and 11 biomarkers concentrations from 4 different physiological systems (inflammatory, metabolic, cardiovascular and sex hormones), considering health behaviours, BMI and reproductive factors and (2) examine the association between BHS and socially stratified biomarkers and BC risk. Our central hypothesis posits that educational attainment influences the levels of BHS and some biomarkers that in turn will be associated with future risk of BC through a biological effect of the social environment, over and above health behaviours, anthropometrics and reproductive factors.

MATERIAL AND METHODS

Study cohort

E3N has been described in detail elsewhere⁵¹ and is part of the European Prospective Investigation into Cancer and Nutrition (EPIC) study.⁵²

Briefly, E3N includes 98 995 women aged 40-75 and insured by the Mutuelle Générale de l'Éducation Nationale

(MGEN), a national health insurance plan that primarily, but not only, covers teachers. At inclusion, participants provided a written informed consent for the study and for MGEN to provide information to the research team. They filled in a questionnaire that collected information about anthropometric measures, lifestyle/behaviours, SEP and health. Self-administered questionnaires have been subsequently sent every 2–3 years since 1990. The June 1993 questionnaire (Q3) included a detailed diet history questionnaire. Between 1994 and 1999, blood samples were collected from approximately 25 000 female volunteers and stored until they were assayed in nested case-control studies, corresponding to the period when the Q4 (1994) and Q5 (1997) questionnaires were sent out (see details on Measures paragraph). During the blood sampling visit, SBP, diastolic blood pressure (DBP) and heart rate (HR) were measured.

Study population

Of the 98 995 women in E3N, we included all women who had at least one biomarker measurement available and who participated in case-control studies that intended to measure biomarkers of the 4 biological systems (inflammatory, metabolic, cardiovascular and sex hormones) (n=3932).

These measurements were made within five nested case-control studies aiming to assess the association between different hormones and diseases (BC, adenoma, melanoma, ovarian cancer and diabetes) in 2008 and 2011. Therefore, population study's selection depends on inclusion criteria of these nested case-control studies (see online supplemental table 1) for a detailed description of the nested case-control studies).

Women who were lost to follow-up or diagnosed with BC prior to blood collection or missing for blood collection's date were removed from the analyses (n=19). Among women with BC after blood collection, those with unconfirmed anatomopathology diagnosis (n=21) were excluded. Those with multiple localisations of cancer, secondary breast localisation (n=13) or Paget disease (n=2) were also excluded because of their risk factors specificity in BC. Women with in situ BC (n=40) were further excluded because of problems in completeness of data collection. Additionally, women in premenopause or with unknown status (N=789) at the time of blood collection were also removed because of early age cancer specificities.

Our study population for the main analyses included 3048 postmenopausal women free of cancer at blood sample collection. The flow chart describing the selection of the study population is given in [figure 1](#).

Main outcomes

BHS and individual biomarkers

A single sample collection protocol has been defined for the EPIC cohort.⁵² From each subject, about 30 mL of blood was drawn, and serum, plasma, erythrocytes, and buffy coat were aliquoted in plastic straws of 0.5 mL each, which were heat-sealed and stored under liquid nitrogen

(−196°C) in a centralised biobank. We included all biomarkers available in the nested case-control studies suspected to be associated with BC risk representing four systems to assess the biological embodiment of SEP: CRP for the inflammatory system; total cholesterol, LDL (low-density lipoprotein), HDL and TG for the metabolic system; SBP, DBP and HR for the cardiovascular system; and testosterone, oestradiol and SHBG for the sex endogenous hormones system.

Biological markers used in this study have been measured in previous case-control studies conducted on E3N cohort and measurements of some of them has been described elsewhere.^{53 54} The majority of the assays were performed at the biochemistry laboratory at the Bichat Hospital (Paris).

Following the most frequent methodology to construct the AL score,¹⁴ quartile-based cut-offs for each biomarker (N=11) were used to identify participants relatively at 'higher risk' for health compared with others.¹³ Therefore, participants were considered at 'higher risk' for a specific biomarker if that biomarker concentration was above the 75th percentile from their respective case-control study (or from the population study for the clinical measures), except for HDL and SHBG whose high-risk cut-points were defined as below the 25th percentile.¹³ For women who have participated in more than one nested case-control study, any missing data were supplemented using information extracted from other nested studies, starting with the second-largest study and progressing accordingly. A conservative approach (maximum bias) was used if the measure was missing in all studies, systematically considering them in the 'lower risk' category.

If a woman was in the 'higher risk' group for a specific biomarker she was given a subscore of 1 for that biomarker, allowing us to sum the subscore of all biomarkers to construct our quantitative BHS (ranging theoretically from 0 to 11).

Breast cancer

In E3N, self-reported BC diagnosis was confirmed through pathological reports. All BC diagnosis from after blood collection to 2014 (last diagnosis date available) were considered regardless of their case-control status from the nested studies. 531 BC cases were diagnosed over 20 years of follow-up.

Main exposure

Educational attainment

We used self-reported educational attainment as our main SEP exposure. This selection stems from its established association with future risk of BC, as indicated by our prior investigation within the E3N cohort.⁷ Women's education was categorised into three groups: less educated women (below baccalaureate (high school diploma)), middle educated women (baccalaureate—2 years of tertiary education) and most educated women (3 years or more of tertiary education).

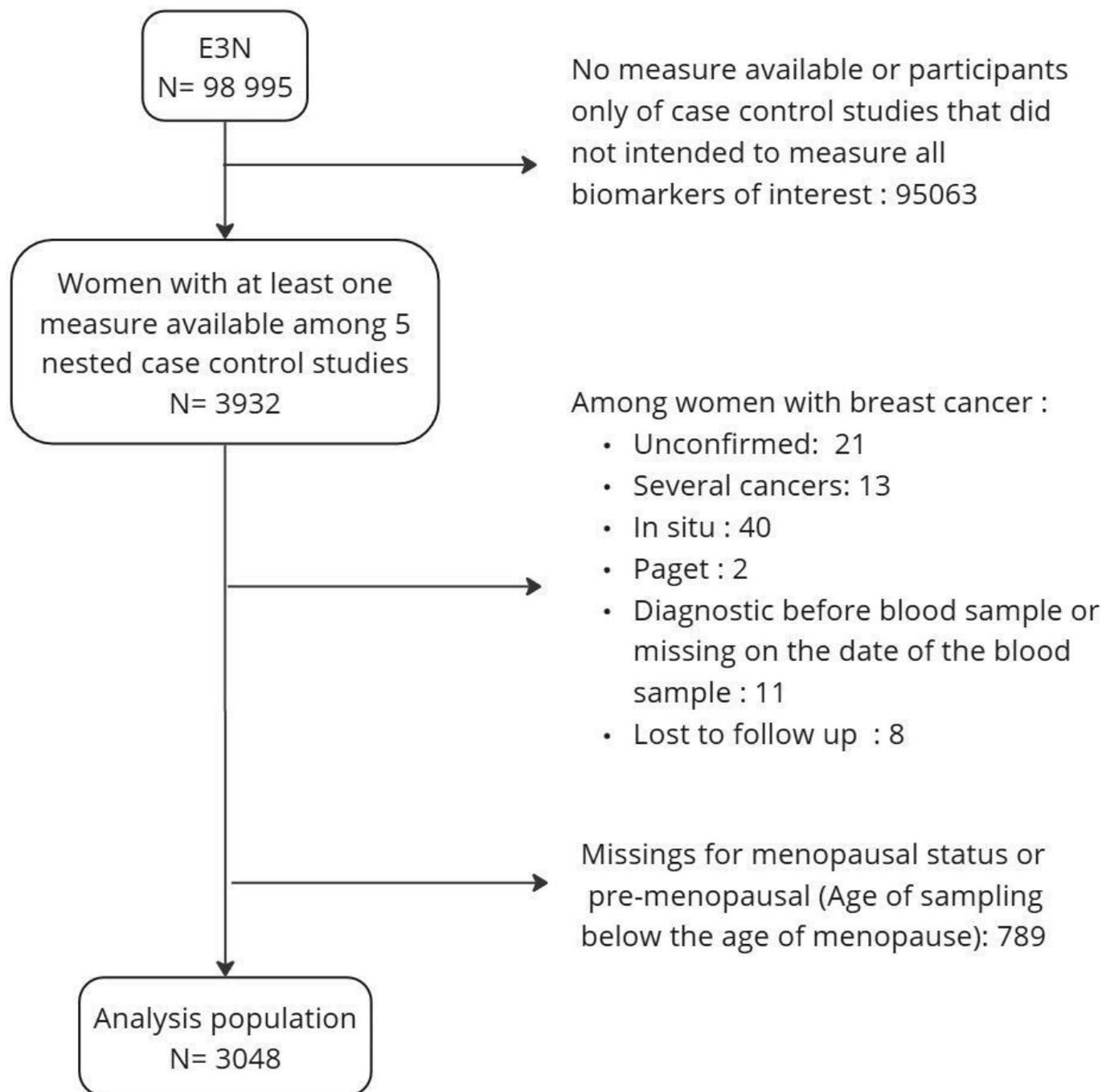


Figure 1 Flow chart of study population selection.

Covariates

Key variables that could act as confounders on the association of each biomarkers and BC risk and could potentially mediate the association between educational attainment and the level of each biomarker were selected a priori based on our previous works.⁷ Median-cuted age at blood sample and original case-control study of participants were also constructed and used as confounders. The other variables were considered as potential mediators and can be categorised into two main categories: health behaviours and anthropometric characteristics including alcohol consumption; smoking status; physical activity; western diet pattern; BMI and reproductive factors

including use of menopausal hormone therapy (MHT); oral contraceptive (OC); age at the first childbirth; age at menarche; cumulative breastfeeding duration; reproductive lifespan. We also included family history of hormone-related cancer and family history of BC.

We selected these intermediate variables from the questionnaire closest to blood sample. For women whose information was not available at the time of blood collection, we used those from previous questionnaires to respect the clear temporal sequence where all intermediate factors precede biological measures.

See online supplemental text 1 for more details on collection and categorisation of covariates.

Statistical analyses

Association between educational attainment and measures BHS and individual biomarkers

For the analysis of social stratification of the BHS and individual biomarkers, we started with a description of the variable distribution within our study population, followed by conducting bivariate analyses. Kruskal-Wallis rank sum test for the BHS and χ^2 tests for each dichotomised biomarker were performed. These analyses were conducted between (1) educational attainment and the BHS, then with each dichotomised biomarker, (2) the educational attainment and each covariate and (3) each dichotomised biomarker and each covariate. For all the analyses, the reference group for educational attainment was the low education group, as it is a priori considered to be at the lowest risk of developing BC.

We performed multiple linear regressions to explore the association between educational attainment and the continuous BHS. We adopted a sequential adjustment method to control for confounding and analyse the effect of intermediate factors on the association between educational attainment and the BHS. Five models were developed:

- ▶ Model 0: Educational attainment+median-cuted age at sampling.
- ▶ Model 1: Model 0+case–control study.
- ▶ Model 1a: Model 1+anthropometric and behavioural factors.
- ▶ Model 1b: Model 1+reproductive factors and family history of hormonal cancer.
- ▶ Model 2: Fully adjusted model (model 1a+1b).

Subsequently, we performed the same analytical approach to study the association between educational attainment and each dichotomised biomarker as the dependent variable in multiple logistic regressions. The reference groups considered for biomarkers was always the 'less at risk' groups.

Given that the results showed a more significant influence on the models' coefficients with the addition of anthropometric and behavioural covariates compared with others, we conducted an in-depth exploration of anthropometric and behavioural covariates, resulting in additional models for each variable within this category. This exploration was carried out adding each covariate separately to model 1 (model 1+tobacco, model 1+physical activity, model 1+diet, model 1+alcohol, model 1+BMI).

Association between BHS, each socially stratified biomarker and BC

To explore the relationship between BHS, each socially stratified biomarker identified in the previous step and BC we first conducted bivariate analyses using the Wilcoxon rank sum and χ^2 test. Given that none of these associations reached significance at the 0.2 threshold, we did not investigate further the relationship between the socially patterned biomarkers and BHS and future risk of BC.

Missing data

To control for possible bias due to missing data in educational attainment and covariates, there were imputed using multiple imputation in the study population with the MICE R package.⁵⁵ 20 imputations were conducted taking the missing-at-random assumption from the study population. All variables considered in the fully adjusted model were employed in the imputation models.⁵⁶

Sensitivity analyses

To test the robustness of our results, we repeated these analyses in a complete cases population (N=2605). To test the association between BHS, each socially stratified biomarkers and BC on a population selected to study BC risk, we repeated the analyses in the BC nested case–control study population⁵⁴ (N=1428).

All analyses were performed with R released V.4.1.3 with the Tidyverse and MICE packages.

Patient and public involvement

None.

RESULTS

Descriptive characteristics of biomarkers and covariates of women from the subcohort E3N by educational attainment are given in [table 1](#) and online supplemental table 2, respectively.

Most of the women had a middle (48%) or higher level of education (39%). Differences by educational attainment were observed for the BHS and for 7 out of 11 biomarkers investigated in bivariate analyses. Women with a higher educational attainment had a lower BHS and were at lower risk of having higher levels of CRP, TG, DBP and SBP and lower levels of HDL and SHBG compared with women with a lower educational attainment. They were at greater risk of having a higher level of oestradiol compared with women with a lower educational attainment ([table 1](#)).

Women with a higher level of education were younger at blood sample collection, were more likely to be ever or former smokers, inactive, taller and thinner and to have a low adherence to a western diet pattern. They were also more likely to have ever used a MHT and an OC, to have been older at first childbirth, to have a longer reproductive lifespan and to breastfeed for a longer duration. They were more likely to develop BC (online supplemental table 2).

Association between educational attainment and the BHS

Results from multivariate regression analyses between educational attainment and the BHS are presented in [table 2A](#) and [figure 2](#).

In the linear regressions' models, after controlling for age and case–control study, women with a higher educational attainment were more likely to have a lower BHS ($\beta_{\text{High}} = -0.40$ (95% CI $-0.62; -0.19$), model 1) compared with women with a lower educational attainment. This

**Table 1** Biological characteristics of women with available data from E3N by educational attainment

		Educational attainment*			Missing N	P value†
		Total	Low N (%)	Middle N (%)		
	Total	3048 (100.0)	367 (12.4)	1432 (48.4)	1157 (39.1)	92
BHS‡						
BHS	Med (IQR)	2.0 (1.0; 4.0)	3.0 (2.0; 4.0)	2.0 (1.0; 4.0)	2.0 (1.0; 4.0)	0.0008
Higher concentration=higher risk						
CRP	Lower risk	2307 (75.7)	254 (69.2)	1089 (76.0)	891 (77.0)	73
	Higher risk	741 (24.3)	113 (30.8)	343 (24.0)	266 (23.0)	19
Cholesterol	Lower risk	2322 (76.2)	282 (76.8)	1094 (76.4)	871 (75.3)	75
	Higher risk	726 (23.8)	85 (23.2)	338 (23.6)	286 (24.7)	17
LDL	Lower risk	2328 (76.4)	278 (75.7)	1085 (75.8)	896 (77.4)	69
	Higher risk	720 (23.6)	89 (24.3)	347 (24.2)	261 (22.6)	23
Triglycerides	Lower risk	2319 (76.1)	264 (71.9)	1092 (76.3)	891 (77.0)	72
	Higher risk	729 (23.9)	103 (28.1)	340 (23.7)	266 (23.0)	20
HR	Lower risk	2292 (75.2)	269 (73.3)	1080 (75.4)	871 (75.3)	72
	Higher risk	756 (24.8)	98 (26.7)	352 (24.6)	286 (24.7)	20
DBP	Lower risk	2292 (75.2)	262 (71.4)	1055 (73.7)	910 (78.7)	65
	Higher risk	756 (24.8)	105 (28.6)	377 (26.3)	247 (21.3)	27
SBP	Lower risk	2291 (75.2)	244 (66.5)	1064 (74.3)	915 (79.1)	68
	Higher risk	757 (24.8)	123 (33.5)	368 (25.7)	242 (20.9)	24
Testosterone	Lower risk	2305 (75.6)	271 (73.8)	1080 (75.4)	892 (77.1)	62
	Higher risk	743 (24.4)	96 (26.2)	352 (24.6)	265 (22.9)	30
Oestradiol	Lower risk	2307 (75.7)	294 (80.1)	1104 (77.1)	846 (73.1)	63
	Higher risk	741 (24.3)	73 (19.9)	328 (22.9)	311 (26.9)	29
Lower concentration=higher risk						
HDL	Lower risk	2323 (76.2)	265 (72.2)	1099 (76.7)	893 (77.2)	66
	Higher risk	725 (23.8)	102 (27.8)	333 (23.3)	264 (22.8)	26
SHBG	Lower risk	2313 (75.9)	263 (71.7)	1056 (73.7)	919 (79.4)	75
	Higher risk	735 (24.1)	104 (28.3)	376 (26.3)	238 (20.6)	17

*Women's education was categorised into three groups: less educated women (below baccalaureate (high school diploma)), middle educated women (baccalaureate—2 years of tertiary education) and most educated women (3 years or more of tertiary education).

†Wilcoxon rank sum and χ^2 test.

‡The biomarkers were quartile transformed in the corresponding case–control study population (except for SBP, DBP and HR, which were transformed relative to the analysis population), and then dichotomised into high risk (subscore 1) and low risk (subscore 0) based on whether the highest quartile exposed to health risk was Q1 (HDL, SHBG) or Q4 (all others). Missing data in all studies were imputed by 0. BHS was calculated by summing all subscore across biomarkers.

§ Bold values indicate p-values that are statistically significant at the 5% threshold.

BHS, Biological Health Score; CRP, C reactive protein; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein; SBP, systolic blood pressure; SHBG, sex hormone-binding globulin.

association was weakened after adjustment for health behaviours and anthropometric measures ($\beta_{\text{High}}=-0.24$ (95% CI -0.45; -0.03), model 1a) and to a lesser extent after adjustment for reproductive factors ($\beta_{\text{High}}=-0.34$ (95% CI -0.56; -0.12), model 1b). The association between educational attainment and the BHS was more strongly weakened in the fully adjusted model, but this does not seem to explain the entire effect with regard to the parameter and confidence interval ($\beta_{\text{High}}=-0.21$ (95% CI -0.42; 0.01), model 2).

Association between educational attainment and each biomarker

Results from multivariate regression analyses between educational attainment and each biomarker are presented in [table 2b](#) and [figure 2](#).

In the logistic regressions' models, after controlling for age and case–control study, women with a higher educational attainment were at lower risk of having higher levels of CRP, TG, DBP, SBP and lower levels of HDL and SHBG (OR_{CRP-high}=0.70 (95% CI 0.54; 0.91), OR_{TG-high}=0.79 (95%

Table 2 Results from (A) multivariate linear regression analyses of the association between education and BHS (B) multivariate logistic regression analyses of the association between education and each biomarker, using data obtained from multiple imputation (N=3048)

Dependent variables	Education level	Univariable model	Model 0	Model 1	Model 1a	Model 1b	Model 2
A. BHS: b coefficients from linear regression (95% CI)							
	Low	–	–	–	–	–	–
	Middle	–0.28 (–0.49 to –0.07)	–0.26 (–0.47 to –0.05)	–0.26 (–0.47 to –0.05)	–0.16 (–0.36 to 0.04)	–0.23 (–0.44 to –0.02)	–0.14 (–0.34 to 0.06)
	High	–0.44 (–0.65 to –0.22)	–0.41 (–0.62 to –0.19)	–0.40 (–0.62 to –0.19)	–0.24 (–0.45 to –0.03)	–0.34 (–0.56 to –0.12)	–0.21 (–0.42 to 0.01)
B. Biomarkers: ORs from logistic regression (95% CI)							
CRP	Low	–	–	–	–	–	–
	Middle	0.70 (0.55 to 0.91)	0.70 (0.55 to 0.91)	0.72 (0.56 to 0.93)	0.79 (0.60 to 1.03)	0.74 (0.57 to 0.97)	0.81 (0.62 to 1.06)
	High	0.67 (0.52 to 0.87)	0.67 (0.52 to 0.87)	0.70 (0.54 to 0.91)	0.82 (0.62 to 1.07)	0.75 (0.57 to 0.99)	0.86 (0.65 to 1.15)
Cholesterol	Low	–	–	–	–	–	–
	Middle	1.03 (0.79 to 1.35)	1.03 (0.79 to 1.35)	1.06 (0.81 to 1.39)	1.10 (0.84 to 1.44)	1.09 (0.83 to 1.44)	1.13 (0.85 to 1.49)
	High	1.08 (0.82 to 1.43)	1.08 (0.82 to 1.43)	1.14 (0.86 to 1.50)	1.23 (0.93 to 1.64)	1.19 (0.89 to 1.59)	1.28 (0.95 to 1.72)
LDL	Low	–	–	–	–	–	–
	Middle	1.01 (0.78 to 1.32)	1.01 (0.78 to 1.32)	1.04 (0.79 to 1.35)	1.09 (0.83 to 1.43)	1.09 (0.83 to 1.43)	1.14 (0.87 to 1.50)
	High	0.92 (0.70 to 1.21)	0.92 (0.70 to 1.21)	0.96 (0.73 to 1.26)	1.04 (0.79 to 1.38)	1.04 (0.78 to 1.39)	1.12 (0.84 to 1.51)
HDL	Low	–	–	–	–	–	–
	Middle	0.79 (0.61 to 1.02)	0.79 (0.61 to 1.02)	0.79 (0.61 to 1.03)	0.84 (0.64 to 1.09)	0.82 (0.63 to 1.06)	0.86 (0.66 to 1.13)
	High	0.77 (0.59 to 1.01)	0.77 (0.59 to 1.01)	0.79 (0.60 to 1.03)	0.84 (0.63 to 1.10)	0.82 (0.62 to 1.09)	0.86 (0.64 to 1.15)
Triglycerides	Low	–	–	–	–	–	–
	Middle	0.79 (0.61 to 1.03)	0.79 (0.61 to 1.03)	0.81 (0.63 to 1.05)	0.87 (0.66 to 1.13)	0.82 (0.63 to 1.07)	0.88 (0.67 to 1.15)
	High	0.76 (0.58 to 0.99)	0.76 (0.58 to 0.99)	0.79 (0.61 to 1.04)	0.88 (0.67 to 1.16)	0.81 (0.62 to 1.08)	0.89 (0.67 to 1.19)
Heart rate	Low	–	–	–	–	–	–
	Middle	0.89 (0.69 to 1.16)	0.89 (0.69 to 1.16)	0.88 (0.68 to 1.15)	0.89 (0.68 to 1.16)	0.89 (0.68 to 1.16)	0.90 (0.69 to 1.17)
	High	0.90 (0.69 to 1.17)	0.90 (0.69 to 1.17)	0.88 (0.67 to 1.15)	0.89 (0.68 to 1.17)	0.87 (0.66 to 1.15)	0.89 (0.67 to 1.18)
DBP	Low	–	–	–	–	–	–
	Middle	0.89 (0.69 to 1.16)	0.89 (0.69 to 1.16)	0.90 (0.69 to 1.16)	0.93 (0.72 to 1.21)	0.89 (0.69 to 1.16)	0.92 (0.71 to 1.20)
	High	0.69 (0.53 to 0.90)	0.69 (0.53 to 0.90)	0.69 (0.53 to 0.90)	0.76 (0.57 to 0.99)	0.70 (0.53 to 0.92)	0.75 (0.57 to 1.00)
SBP	Low	–	–	–	–	–	–
	Middle	0.69 (0.54 to 0.88)	0.69 (0.54 to 0.88)	0.72 (0.56 to 0.92)	0.75 (0.58 to 0.97)	0.72 (0.56 to 0.93)	0.75 (0.57 to 0.97)

Continued



Table 2 Continued

Dependent variables	Education level	Univariable model	Model 0	Model 1	Model 1a	Model 1b	Model 2
Testosterone	High	0.53 (0.41 to 0.68)	0.53 (0.41 to 0.68)	0.57 (0.44 to 0.74)	0.62 (0.47 to 0.81)	0.58 (0.44 to 0.76)	0.61 (0.46 to 0.81)
	Low	–	–	–	–	–	–
	Middle	0.92 (0.71 to 1.20)	0.92 (0.71 to 1.20)	0.91 (0.70 to 1.18)	0.93 (0.72 to 1.22)	0.92 (0.70 to 1.19)	0.93 (0.71 to 1.22)
Oestradiol	High	0.84 (0.64 to 1.10)	0.84 (0.64 to 1.10)	0.82 (0.63 to 1.08)	0.85 (0.65 to 1.13)	0.83 (0.62 to 1.10)	0.85 (0.64 to 1.13)
	Low	–	–	–	–	–	–
	Middle	1.20 (0.90 to 1.59)	1.20 (0.90 to 1.59)	1.13 (0.84 to 1.51)	1.10 (0.82 to 1.48)	1.06 (0.79 to 1.44)	1.05 (0.77 to 1.42)
SHBG	High	1.47 (1.10 to 1.96)	1.47 (1.10 to 1.96)	1.34 (1.00 to 1.79)	1.26 (0.94 to 1.70)	1.26 (0.92 to 1.71)	1.21 (0.89 to 1.66)
	Low	–	–	–	–	–	–
	Middle	0.91 (0.70 to 1.17)	0.91 (0.70 to 1.17)	0.92 (0.71 to 1.19)	1.04 (0.79 to 1.37)	0.97 (0.75 to 1.27)	1.11 (0.84 to 1.46)
SHBG	High	0.66 (0.5 to 0.86)	0.66 (0.50 to 0.86)	0.67 (0.52 to 0.88)	0.81 (0.61 to 1.08)	0.75 (0.57 to 0.99)	0.89 (0.66 to 1.20)
	Low	–	–	–	–	–	–
	Middle	0.91 (0.70 to 1.17)	0.91 (0.70 to 1.17)	0.92 (0.71 to 1.19)	1.04 (0.79 to 1.37)	0.97 (0.75 to 1.27)	1.11 (0.84 to 1.46)

Reference= 'Lower risk'

Model 0: Adjusted for age at blood sample- Model 1: Adjusted for age and case control study. - Model 1a : Model 1 + anthropometric and behavioural factors (smoking status, physical activity, alcohol consumption, western diet, BMI) - Model 1b : Model 1 + reproductive factors (age at menarche, Family history of hormone related cancer, family history of breast cancer, oral contraception, menopausal hormone therapy, age at first childbirth, breastfeeding duration, reproductive lifespan) - Model 2 : Complete model

BHS, Biological Health Score; BMI, body mass index; CRP, C reactive protein; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; SHBG, sex hormone-binding globulin.

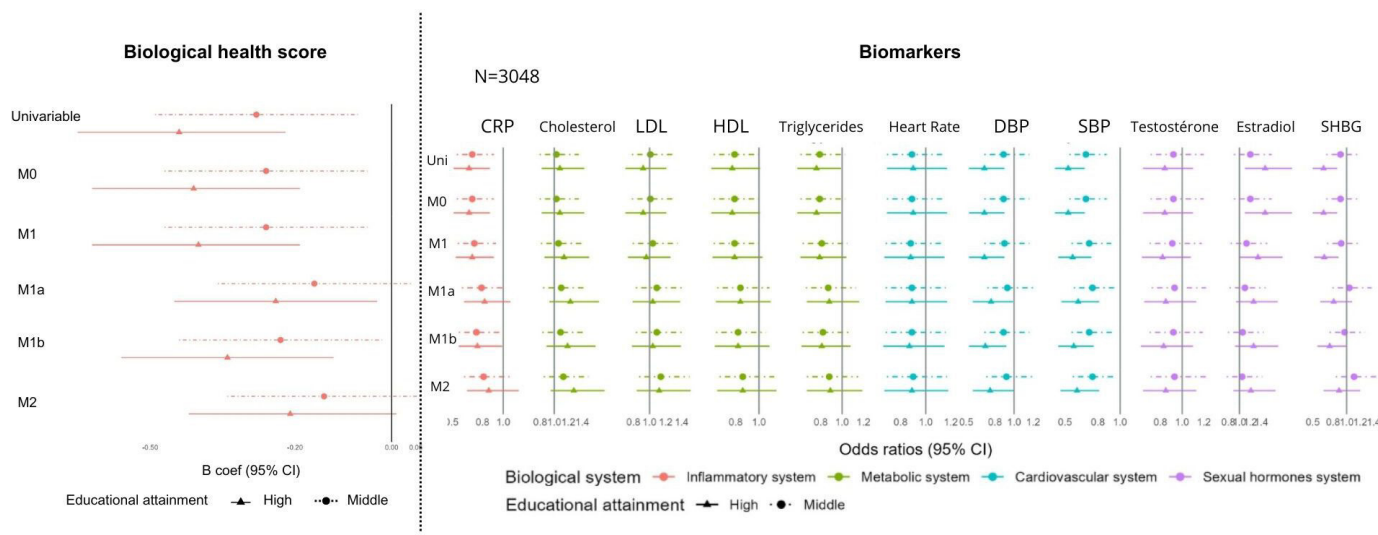


Figure 2 Forest plot of linear regression models for the BHS and forest plot of logistic regression models for each biomarker on imputed data (N=3048). Solid lines represent women with average educational attainment and dotted lines represent women with high educational attainment. The reference is the low educational attainment group, and for the biomarkers the least-at-risk category. Univariable=without adjustment, M0=adjustment for age at sampling, M1=M0+case-control study, M1a=M1+behavioural and anthropometric factors (tobacco, diet, BMI, physical activity), M1b=M1+reproductive factors (age at first menstruation, age at first child, reproductive lifespan, Hormone replacement therapy, Oral contraception, family history of hormone-dependent cancers and breast cancer, duration of breastfeeding), M2=Fully adjusted model. BHS, Biological Health Score; BMI, body mass index; BP, blood pressure; C reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SHBG, sex hormone-binding globulin.

CI 0.61; 1.04), OR_{DBP-high}=0.69 (95% CI 0.53; 0.90), OR_{SBP-high}=0.57 (95% CI 0.44; 0.74), OR_{HDL-high}=0.79 (95% CI 0.60; 1.03), OR_{SHBG-high}=0.67 (95% CI 0.52; 0.88); model 1) than women with a lower educational attainment. They were at greater risk of having higher levels of oestradiol (OR_{Oestradiol-high}=1.34 (95% CI 1.00; 1.79)).

Associations with CRP, HDL, TG, SHBG and oestradiol were weakened after adjustment for health behaviours and anthropometric measures (OR_{CRP-high}=0.82 (95% CI 0.62; 1.07), OR_{TG-high}=0.88 (95% CI 0.67; 1.16), OR_{HDL-high}=0.84 (95% CI 0.63; 1.10), OR_{SHBG-high}=0.81 (95% CI 0.61; 1.08), OR_{Oestradiol-high}=1.26 (95% CI 0.94; 1.70); model 1A) and to lesser extent after adjustment for reproductive factors ((OR_{CRP-high}=0.75 (95% CI 0.57; 0.99), OR_{TG-high}=0.81 (95% CI 0.62; 1.08), OR_{HDL-high}=0.82 (95% CI 0.62; 1.09), OR_{SHBG-high}=0.75 (95% CI 0.57; 0.99), OR_{Oestradiol-high}=1.26 (95% CI 0.92; 1.71); model 1B) and in the fully adjusted model ((OR_{CRP-high}=0.86 (95% CI 0.65; 1.15), OR_{TG-high}=0.89 (95% CI 0.67; 1.19), OR_{HDL-high}=0.86 (95% CI 0.64; 1.15), OR_{SHBG-high}=0.89 (95% CI 0.66; 1.20), OR_{Oestradiol-high}=1.21 (95% CI 0.89; 1.66), model 2).

Associations between educational attainment and SBP or DBP were weakened but still statistically significant notably for high educational attainment, after adjustment for health behaviours and anthropometric measures (OR_{DBP-high}=0.76 (95% CI 0.57; 0.99), OR_{SBP-high}=0.62 (95% CI 0.47; 0.81); model 1A) and to lesser extent after adjustment for reproductive factors (OR_{DBP-high}=0.70 (95% CI 0.53; 0.92), OR_{SBP-high}=0.58 (95% CI 0.44; 0.76); model 1B) and in the fully adjusted model (OR_{DBP-high}=0.75 (95% CI 0.57; 1.00), OR_{SBP-high}=0.61 (95% CI 0.46; 0.81); model 2).

Additional analyses

Whether we look at biomarkers or the BHS, the addition of 'smoking', 'physical activity', 'alcohol consumption' or 'western diet' to model 1 independently has almost no effect on the coefficients (ORs or β s) in contrast to BMI, which had a stronger effect on the results: the addition of BMI attenuated the association between education and biomarkers/BHS (online supplemental table 3).

Association between biomarkers and future risk of BC

In our study population, 17% of women had BC. There was no association in our analysis between BHS and BC and no associations between socially stratified biomarkers and BC (table 3).

Sensitivity analysis

Complete-case analyses showed similar results between educational attainment and each biomarker and the BHS. Moreover, we found that the effect of educational attainment was weaker for three biomarkers (CRP, DBP and oestradiol; online supplemental table 4). Analyses on the BC case-control study showed no association between BHS, socially stratified biomarker and BC except for women with low SHBG (31% among the control group vs 35% among cases), but the association was not statistically

significant at a 5% threshold ($p=0.10$; online supplemental table 5).

DISCUSSION

The current study examined the association between SEP operationalised as educational attainment and a set of biomarkers taken individually and combined through a BHS, a known risk factor for many health outcomes.

We found that women with higher educational attainment were at lower biological risk compared with women with a lower educational attainment. Among the 11 biomarkers investigated, 7 biomarkers (CRP, HDL, TG, SBP, DBP, oestradiol and SHBG) related to inflammatory, metabolic, cardiovascular and hormonal physiological systems were socially distributed. We also undertook a thorough examination of a diverse array of intermediates variables with varying characteristics, including behavioural, anthropometric and reproductive factors. For BHS and the seven socially stratified biomarkers, all associations were partially explained by anthropometric and reproductive variables. Association between education and BHS persisted even after adjustment for behavioural, anthropometric and reproductive measures. Regarding individual biomarkers, when all the intermediate variables were considered simultaneously, only the relationships between educational attainment SBP and DBP were still statistically significant after adjustment: women with a higher educational attainment were at lower risk to have a high SBP or DBP compared with women with a lower educational attainment. No evidence of an association between BHS or socially stratified biomarkers and BC risk was identified.

The BHS pattern by educational attainment is consistent with previous literature that linked either the BHS or the AL with different socioeconomic indicators.¹⁴⁻¹⁶ In 2017, a systematic review conducted on 26 both longitudinal and cross-sectional studies in 7 countries and in majority in the USA, Johnson *et al* showed that the AL scores were higher for the less advantaged (assessed by multiple SEP measures) in all but 3 studies, even if all of them did not adjust for behavioural measures.¹⁴ Later on, Karimi *et al*¹⁵ and Neufcourt *et al*¹⁶ showed a higher BHS for the less educated in the UK and in the Norway context, even after adjustment for health behaviours. Our study provides additional evidence by revealing the same pattern in the French context, in postmenopausal women.

To better understand how educational attainment relates to the BHS, we considered various intermediate variables that might influence this relationship. As we accounted for behavioural, anthropometric and reproductive variables, the link between educational attainment and biological health became weaker. Notably, BMI, well known to be higher in the less socially advantaged,⁵⁷ emerged as a particularly important potential mediator of the association between educational attainment and the BHS among French women, in lines with

**Table 3** BHS and biomarkers distribution by BC status

		Total N (%)	BC status		P value†
			No N (%)	Yes N (%)	
	Total	N=3048 (100.0)	N=2517 (82.6)	N=531 (17.4)	
BHS*	Med (IQR)	2.0 (1.0; 4.0)	2.0 (1.0; 4.0)	2.0 (1.0; 4.0)	0.9901
Biomarkers					
CRP	Lower risk	2307 (75.7)	1911 (82.8)	396 (17.2)	0.5107
	Higher risk	741 (24.3)	606 (81.8)	135 (18.2)	
HDL	Lower risk	2323 (76.2)	1909 (82.2)	414 (17.8)	0.2967
	Higher risk	725 (23.8)	608 (83.9)	117 (16.1)	
Triglycerides	Lower risk	2319 (76.1)	1911 (82.4)	408 (17.6)	0.6542
	Higher risk	729 (23.9)	606 (83.1)	123 (16.9)	
DBP	Lower risk	2292 (75.2)	1886 (82.3)	406 (17.7)	0.4585
	Higher risk	756 (24.8)	631 (83.5)	125 (16.5)	
SBP	Lower risk	2291 (75.2)	1886 (82.3)	405 (17.7)	0.5158
	Higher risk	757 (24.8)	631 (83.4)	126 (16.6)	
Oestradiol	Lower risk	2307 (75.7)	1905 (82.6)	402 (17.4)	0.9919
	Higher risk	741 (24.3)	612 (82.6)	129 (17.4)	
SHBG	Lower risk	2313 (75.9)	1918 (82.9)	395 (17.1)	0.3746
	Higher risk	735 (24.1)	599 (81.5)	136 (18.5)	

Only biomarkers previously associated with educational attainment at $p < 0.2$ were considered.

*Biomarkers were quartile-transformed from their corresponding case-control study population (except for SBP, DBP and HR which were transformed from analyses population) and then dichotomised into Higher risk (subscore 1) and lower risk (subscore 0) depending on whether the quartile most at risk for health was Q1 (HDL, TG, SHBG) or Q4 (all others). Missing data in all studies were imputed by 0. BHS was calculated by summing all the subscores across biomarkers.

†Wilcoxon rank sum and Pearson's χ^2 tests.

‡ Bold values indicate p-values that are statistically significant at the 5% level

BC, breast cancer; BHS, Biological Health Score; CRP, C reactive protein; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HR, heart rate; SBP, systolic blood pressure; SHBG, sex hormone-binding globulin; TG, triglycerides.

previous literature.¹⁵ This important attenuation can be explained primarily by a significant correlation between BMI and the biomarkers used to construct the BHS. It has been demonstrated that obesity, and more specifically, excess adipose tissue, is associated with the activation of numerous inflammatory pathways, leading to increased CRP levels, especially in women.^{58 59} Cardiometabolic dysregulation resulting in higher levels of LDL, TG, lower levels of HDL^{60 61} and elevated blood pressure^{62 63} has also been observed. In postmenopausal women, adipose tissue is additionally a significant producer of oestrogens.^{64 65}

Second, numerous studies have hypothesised that BMI, like other measures approximating level of adipose tissue (waist-hip ratio, percentage of body fat), could serve as a biomarker for the metabolic system.¹⁴ According to the systematic review by Johnson *et al*,²⁴ out of 26 studies have used either BMI, waist circumference, waist-hip ratio or per cent body fat directly in AL calculation.¹⁴ Since it captures similar aspects as a portion of BHS, adjusting for BMI attenuates the relationship between social position, BHS or biomarkers in our study. We use BMI as an

adjustment factor, assuming that it is a distinct measure which do not only captures body composition but is also a multidimensional, multisystem and complex measure.

Less educated women exhibit a higher level of two biomarkers from the cardiovascular system: DBP and SBP. These findings align with existing literature.^{23–25} The contribution of our study lies in the persistence of these differences across all socioeconomic groups even after adjusting for behaviours, anthropometric and reproductive factors. These results may support the hypothesis that social position may lead to chronic psychosocial stress that overstimulates the hypothalamic-pituitary-adrenal axis (HPA).^{10 19} This axis is closely linked to blood pressure, as it increases the secretion of hypertensive hormones (cortisol, epinephrine and norepinephrine) and also over activates the sympathetic autonomic nervous system and decrease parasympathetic regulation.^{10 66} Therefore, it can be hypothesised that the association between education and DBP/SBP may be due to psychosocial exposures that we have not accounted for in our analyses.

Regarding inflammation, SEPs have previously been linked to chronic over activation of stress response mechanisms⁶⁷ (through HPA axis). Higher educational attainment may act as a physiological stress-regulating buffer by increasing the sense of control⁶⁸ which could modulate the association between education and inflammation. Regarding sex hormones, they are the end product of the hypothalamus–pituitary–gonadal (HPG) axis. It has been shown a reciprocal relationship between HPA and HPG, wherein the activation of one affects the function of the other and vice versa.⁶⁹ Despite divergent effects on hormones following the interaction between HPA and HPG, some evidence highlighted an association between stress and higher level of testosterone^{70–72} that may be explained by an overstimulation of the adrenal glands by hyperactivity of the HPA axis.^{73 74} However, we did not establish a social stratification for testosterone, unlike for oestradiol conversely to literature.²⁹ More socially advantaged women tend to have higher oestradiol levels even after accounting for all considered factors. For SHBG, we did not find a significant reduction among more socially advantaged women, contrasting with other studies,^{32 33} while more socially advantaged women exhibited a lower risk of elevated SHBG levels.

Interpretation is more intricate for metabolic factors. The fact that the most educated women in our study have a lower risk of having low HDL levels and high TG levels is consistent with the literature, although some studies have found that these associations are not fully explained by behaviours.^{27 28} It is particularly interesting to note that, apart from BMI, behaviours almost do not explain the relationship between education and these metabolic markers in our study. As explained earlier, BMI is a measure that goes beyond health behaviours and is strongly linked to the metabolic and stress response systems.

In our study, we did not detect any statistically significant association between the BHS or each socially stratified biomarkers and future risk of BC. One potential explanation is that each biomarker used in constructing the BHS may not be uniformly associated with the risk of BC, and that these biomarkers might lack specificity for BC. Yet, two recent studies suggest that elevated AL levels are indeed associated with an increased risk of BC even after adjustment for known risk factors of BC.^{75 76} Despite appearing contradictory to the common observation of higher AL levels in socioeconomically disadvantaged populations¹⁴ and a higher incidence of BC in more privileged women,⁷ this finding could potentially help to explain the more rapid increase in BC incidence among disadvantaged women, like black women in the USA, compared with white women.⁷⁷

The low difference in BC incidence between social groups observed in our study can be partly explained by the relationship that each biomarker has with BC risk. All biomarkers, except for oestradiol, are at higher BC risk concentrations for disadvantaged women. Therefore, higher oestradiol levels in socially advantaged women could be counterbalanced by lower risk levels of

other BC-related biomarkers, and vice versa for disadvantaged women. If oestradiol has a greater impact or is more specific to BC, the difference in risk between social groups could be diminished. One could also hypothesise that the disparity in BC incidence by educational attainment levels would be even more pronounced if biological risk factors on one hand and behavioural and reproductive factors on the other did not offset each other. As illustrated in online supplemental table 6, more educated women, despite having lower body burden of BHS, exhibit a higher prevalence of most behavioural or reproductive risk factors for BC. Overall, women who developed BC could be either more educated women with lower AL and higher reproductive and behavioural risks factors or less educated women with higher AL and lower reproductive and behavioural risks factors. This could explain the lack of differences in cancer risk by educational attainment, and also the absence of biological differences between cases and non-cases of BC in our study.

This work was conducted on a subset of a large prospective cohort of French women in which there is a wide array of biomarkers. A very large number and breadth of intermediate factors were also available. Our method ensured that social (evaluated at baseline and remaining unchanged over time), behavioural and reproductive exposures preceded biological measurements. The prospective design limits both recall and reverse causation biases. Women have been followed since blood collection (1995–1997) until now, which allows us to have a long view of the disease development. Self-reported cancer cases were validated limiting misclassification. We observe a dose–effect relationship for nearly all biological outcomes by educational attainment. Results were consistent from multiple imputation compared with complete-case analysis. Limitations should also be kept in mind. Although the cohort also includes administrative and maintenance staff, the average educational level of the cohort is higher compared with the general population, with less variability in terms of education. In 2020, according to the French Institute of Statistics and Economic Studies, the percentage of women with educational attainment beyond high school was approximately 40%–50% in the same age range as the French population, whereas it was around 90% in our study population (ages 45–75).⁷⁸ At the time of blood collection, around 1995, although this percentage is not available in official data for women, 63% of general population had an educational attainment beyond high school, according to education ministry of France⁷⁹ while in our study 87% of women had an educational attainment beyond high school. Moreover, measures of biomarkers have been made within different case–control studies nested in the E3N cohort conducted in the 2000s, with specific objectives and inclusion criteria which may suggest that our sample is not representative of the whole E3N population. We cannot rule out selection bias even after adjustment for case–control studies of the participants. Considering the BC and cancer-free population



(N=83 436), women with biomarker measurements were more educated, smoked less, were slightly more physically active, participated in screening and had a more frequent history of cancer. The same observations were made when comparing the characteristics of women who volunteered to participate in the biobank versus those who declined the invitation. The population selection bias arisen from E3N design and within E3N could mask or underestimate inequalities and limit the generalisability of our findings.

The specific data collection from nested case-control studies also prompted us to dichotomise biomarker levels as they were not quantitatively comparable probably causing information loss.

We had biomarkers measurements for only one single serum sample for each woman, so we were not able to evaluate intraindividual variability of biomarkers over time. However, it has been shown a good correlation and little intraindividual variation for some biomarkers between two measures.⁸⁰

Additionally, some factors beyond behavioural and anthropometric or reproductive factors that we have not considered here can influence biomarker levels (medications, illnesses) or cancer's risk (exposure to potential carcinogenic environmental exposure or genetic causes).

Results from our study have enhanced the understanding of the link between education and biological functioning by exploring the social to biological transition in a subsample of French women. Studies with greater social variability, larger sample size and a more appropriate biological measures, repeated measurements and with further psychosocial exposition over the life course are necessary to better understand the impact of social exposures and their biological incorporation on health.

A future perspective of this work involves investigating the link between socioeconomic and biomarker involved in cancer's characteristics. Some studies indicate that less educated women might have a higher risk of developing higher grade BC.⁸¹ While it is conceivable that later diagnosis in underprivileged women could explain this observation, it is also plausible that the biological embodiment of the social environment impacts the biological dysregulation of cancer, as suggested by the study of Symonds *et al* on cervical cancer.⁸² Hence, although women with lower educational attainment have a lower risk of BC, they might develop more aggressive forms, given their higher likelihood of dying from BC than more advantaged women. Possibly, socially stratified biomarkers more 'at risk' for less-educated women constitute risk factors for more severe forms of BC.⁸³

In-depth survival analyses should also be carried out. Exploring the risk of developing other cancer type, which could affect all individuals and for which few behavioural and anthropometric factors seem to

be involved, based on exposure to socially stratified biomarkers could further broaden our analysis.

CONCLUSION

This study shows that various biomarkers, as well as a measure of overall biological functioning, are socially distributed, with women with a high and medium level of education having a lower BHS than women with a lower level of education, without this link being fully explained by behavioural and reproductive factors. Moreover, most of the studied biomarkers used to define BHS are socially stratified, even after accounting for behavioural, anthropometric and reproductive intermediate variables, notably for blood pressure. As such, it provides further evidence of the potential impact of social circumstances on our biological functioning. Finally, no associations were found between biomarkers and BC in this study. Further studies are needed to specifically investigate the relationships between socially stratified biomarkers and BC risk.

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