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HEALTH INFORMATION

HISLINK

Mediating effect of health literacy on the relationship between socioeconomic status and health(-related) outcomes

FINABA BERETE • RANA CHARAFEDDINE • STEFAAN DEMAREST • JOHAN VAN DER HEYDEN

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HISlink

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Finaba Berete[1]

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Johan Van der Heyden[1]

•

Rana Charafeddine[1]

•

Stefaan Demarest[1]

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1 Sciensano, Epidemiology and public health, Health information, Brussels

Contact person: Finaba Berete • T+32 2 642 54 76 • Finaba.berete@sciensano.be

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TABLE OF CONTENTS

1. ABSTRACT

Socioeconomic status (SES) is an important determinant of health inequalities between population subgroups. Health literacy (HL) has been hypothesized as one of the mediators in the pathway through which SES affects health(-related) outcomes (HRO). Therefore, in the attempt of reducing socioeconomic health inequalities and investigating its determinants, many factors must be taken into account, including SES and HL.

In this exploratory study, the linkage between the Belgian health interview survey (BHIS) data and the Belgian health compulsory insurance (BCHI) data is used to examine the relationship between SES as measured by educational attainment and household income, and a subset of IMA-based indicators that are of interest from a public health perspective in different domains, namely preventive healthcare (preventive dental care, cancer screening, vaccination), health quality-adequation (use of antibiotics), health quality-continuity (having a global medical record (GMR) and mental health care (use of antidepressants). The main purpose of the study is to investigate the mediating effects of HL in the pathway between SES and these HRO indicators. More specifically, the study aimed to explore:

1) The association between HL and the SES
2) The association between SES and the selected HRO
3) The association between HL and the HRO
4) The mediating effects of HL in the relationship between SES and HRO.

The results of the study can be summarised as follows:

- Overall, HL was positively associated with both educational attainment and household income, indicating that individuals with a higher SES have a higher likelihood of a sufficient level of HL.
- There were significant associations between SES and the investigated HRO but these varied across the outcomes in terms of direction and magnitude. A low SES was associated with a lower probability of preventive dental care and a lower probability of breast cancer screening, while a low SES was associated with a higher probability of having a GMR, use of antibiotics, and use of antidepressants. There was not significant association between SES variables and vaccination against flu.
- Preventive dental care, having a GMR and use of antibiotics are more strongly correlated with educational attainment than with household income. In contrast, use of antidepressants and breast cancer screening are more strongly correlated with household income than with educational attainment.
- Lower HL is associated with lower probability of preventive dental care, higher probability of use of antidepressants and higher probability of being vaccinated against flu.
- Regarding the mediating role of HL in the relationship between SES and HRO, the findings suggest that HL constitutes one of the possible pathways by which SES influence the use of preventive dental care and the use of antidepressants. However, the mediated percentages are quite low (3% and 10% respectively).
- There was no significant mediating contribution of HL in the pathway by which SES affects having a GMR, use of antibiotics, vaccination against flu and breast cancer screening.

In summary, the results of this study indicate that the associations between SES and HRO varied across the outcomes in terms of direction and magnitude where low SES was associated with a lower probability of preventive dental care and breast cancer screening, and with a higher probability of having a GMR, use of antibiotics, and use of antidepressants. Insufficient level of HL is associated with a lower probability of preventive dental care, but with a higher probability of use of antidepressants and higher probability of being vaccinated against flu. HL partially mediates the association between SES and preventive dental care and use of antidepressants, suggesting that improving HL might reduce SES disparities in these areas. The low percentage mediated for the use of antidepressants might suggest a shared decision between physician and patients. No mediating effects were found for vaccination against flu and breast cancer screening, indicating a possible influence of the universal health coverage in place. Further analyses are needed to confirm our results and to better explore the mediating effects of HL in other domains such as lifestyle, health status, and health care use.

2. ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical classification system
BCHI	Belgian Compulsory Health Insurance
BHIS	Belgian Health Interview Survey
CDE	Control Direct Effect
CI	Confidence Interval
DDD	Daily Defined Dose
DPP	Dose Per Package
GMR	Global Medical Record
HL	Health literacy
HRO	Health Related Outcomes
IMA	InterMutualistic Agency
NDE	Natural Direct effect
NIE	Natural Indirect Effect
NIHDI	National Institute for Health and Disability Insurance
OR	Odds Ratio
PM	Percentage Mediated
SD	Standard Deviation
SES	Socioeconomic status
TE	Total Effect
WHO	World Health Organisation

3. INTRODUCTION

4.1 Context

There is strong evidence that socioeconomic status (SES) is an important determinant of health disparities between different population groups, with a low SES being associated to poorer health conditions and behaviours (1–3). Several factors and mechanisms have been proposed to explain the chain of events linking SES to health outcomes (2), including material circumstances like living and working conditions, behavioural factors, social cohesion and social capital, as well as psychological factors like stress, social comparison, lack of social support and inter- and interpersonal resources. However, the entire pathway by which SES exerts its effect on health has not yet been completely clarified (4).

Among these factors, health literacy (HL) has been hypothesized as a potential mediator in the pathway through which SES affects health (5–10), especially when individual judgement and decision making are necessary, such as in the domains of physical activity and nutritional habits (11) or self-rated health status (8,9,12,13). According to the European Health Literacy Survey (HLS-EU) Consortium and the Health promotion glossary 2021, “Health literacy is linked to literacy and entails people’s knowledge, motivation and competences to access, understand, appraise, and apply health information in order to make judgments and take decisions in everyday life concerning healthcare, disease prevention and health promotion to maintain or improve quality of life during the life course” (14,15).

HL is an important factor when assessing public and personal health outcomes. A number of studies showed associations between individuals with low levels of HL and poorer health conditions (16,17), more frequent use of health services, longer hospitalisations (16,18) and higher mortality (17,19). Moreover, a weaker HL has also been associated with unhealthy behaviours, such as smoking (20,21), low physical activity (21,22) and less use of preventive services (17,20). Furthermore, HL has been shown to be associated with socioeconomic status (SES) such as educational attainment, income, material and social deprivation, unemployment, occupation, etc. as well as sociodemographic profile (sex, age, etc.). In view of this, HL is considered by the WHO as an important social determinant of health, influenced by socioeconomic and cultural characteristics and by the functioning of the health systems.

Therefore, in the attempt of reducing SES health inequalities and investigating its determinants, many factors must be taken into account, including both SES and HL. To implement interventions that might reduce health inequities, it is important from a policy perspective to estimate the amount of the total causal effect that is due to the mediation of HL in the relationship between SES and health outcomes. However, empirical research investigating the contribution of HL in this relationship remains scarce.

In Belgium, equity in the use of healthcare resources is an important concern of the National Institute for Health and Disability Insurance (NIHDI). Therefore, insights are needed to understand which factors play a role in inequities in healthcare access. From this perspective, the NIHDI is interested in exploring the mediating effect of HL in the association between SES as measured by educational attainment and household income and heath (-related) outcomes (HRO). A subset of domains and indicators that are selected to explore this and are of great

interest to policy makers are preventive healthcare (preventive dental care, cancer screening, vaccination), health quality-adequation (use of drugs such as antibiotics), health quality-continuity (proportion of the population with global medical records (GMR)) and mental health care (use of antidepressants). The distinction between direct and indirect (mediated) components of the effect of a treatment or exposure (SES variables in this case) on an outcome is quite relevant from a policy perspective to reduce SES health inequalities.

This study aimed to examine the associations between educational attainment, household income, HL and the HRO mentioned above, and to determine whether HL mediates the associations between these SES variables and the health care outcomes. Therefore, the objectives are as follows:

1) explore the association between HL and the SES
2) examine the association between SES and the selected HRO
3) examine he association between HL and the HRO
4) investigate the mediating effects of HL in the relationship between SES and HRO

4.2 Overview of mediation analysis: definitions and concepts

Mediation analysis

Mediation analysis is a method used to understand how and why an independent variable (X) transmits its effect to an outcome (Y) through a mediator (M) (23). The independent variable is also called treatment variable or exposure (in epidemiology). Mediation analysis investigates the mechanisms that underlie an observed relationship between an exposure variable and an outcome variable and examines how they relate to a third intermediate variable, the mediator (24). Rather than hypothesizing only a direct causal relationship between the independent variable and the dependent variable, a mediational model hypothesizes that the exposure variable causes the mediator variable, which in turn causes the outcome variable. The mediator variable then serves to clarify the nature of the relationship between the exposure and outcome variable (25).

Causal diagrams

Mediation is the process through which an exposure causes disease. Researchers can be interested in examining the total effect (TE) of exposure on outcome. However, researchers may also hypothesize that some or all of the TE of exposure on an outcome operates through a mediator, which is an effect of the exposure and a cause of the outcome. When a mediator is hypothesized, the TE can be broken down into two parts: the direct (sometimes called natural direct effect, NDE) and indirect effect (sometimes called natural indirect effect, NIE). The direct effect is the effect of exposure on the outcome absent the mediator (direct pathway: X →Y). The indirect pathway (mediated pathway: X → M → Y) is the effect of exposure on the outcome that works through the mediator. Therefore, mediation analysis decomposes the total exposure outcome effect (i.e., the c path in Figure 1) into an indirect effect estimate and a direct effect (25). The indirect effect quantifies the part of the TE that is transmitted by the mediator (i.e., the a and b paths in Figure 1). The direct effect is the remaining part of the TE estimate that is not transmitted by the mediator (i.e., the c' path in Figure 1) (26).

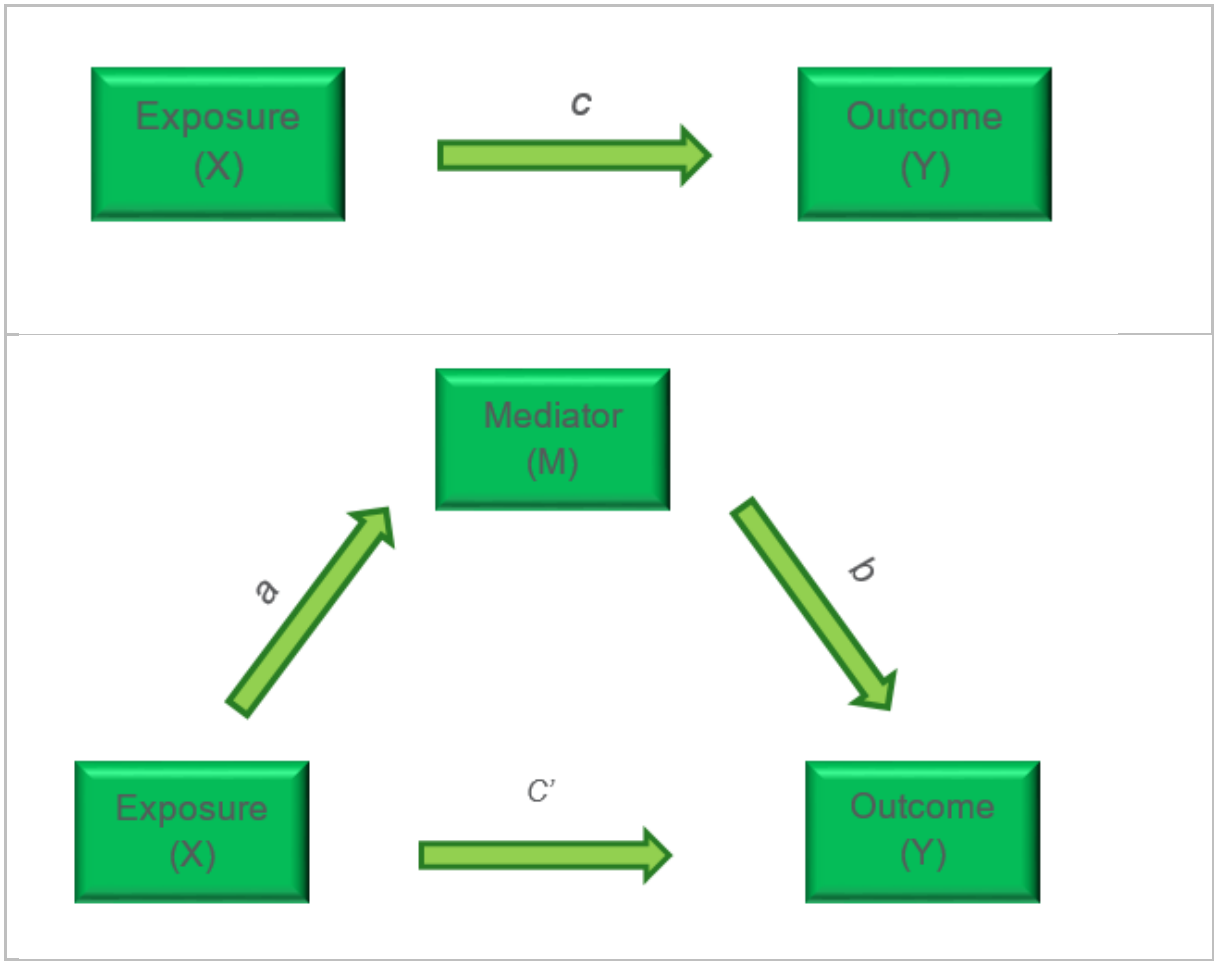

Figure 1: Path diagram of the single mediation model

Estimation approaches, conditions for mediation analysis and steps in estimating mediation effects in single mediation model

Further details about the estimation approaches, conditions and steps in estimating mediation effects can be found in the supplementary files.

In summary, two approaches are used in mediation analysis:

1. the classic regression approach to mediation analysis, strongly influenced by the work of Baron and Kenny (27) has been largely used in psychology and social sciences;
2. the counterfactual approach (28) to mediation analysis or causal mediation (29).

While the traditional approach has important limitations (e.g., it lacks a general framework to define causal mediation and related effects, it does not take into account the interaction effect between treatment and mediator, and it does not explain the assumptions and identification conditions for valid causal effect estimation) (28,30), the counterfactual approach offers solutions to those limitations (28). Within this framework, direct and indirect effects are well defined in terms of counterfactual outcomes (29,31,32).

The main features (constructs) from mediations analysis are (30):

Total effect (TE)

The total effect (TE) for a subject is defined as the difference between the counterfactual outcomes at the treatment and control levels.

Naturel direct effect (NDE)

The natural direct effect (NDE) for a subject is defined as the difference between the counterfactual outcomes at the two treatment levels when an intervention sets the mediator value to M = M0, which is the natural level of the mediator when there is no treatment.

Naturel indirect effect (NIE)

The natural indirect effect (NIE) for a subject is defined as the difference between the counterfactual outcomes at the two mediator levels at M1 and M0 when an intervention sets the treatment to T = 1.

Percentage mediated (PM)

The PM is the percentage of total effect that is mediated.

Other useful constructs can be found in the supplementary data.

The mediation effect analysis needs to meet the following conditions (11,25,28): (1) the exposure variable is significantly associated to the mediator (i.e., a path, from X to M in Figure 1), (2) there is a significant relationship between the mediator and the outcome (i.e., b path, from M to Y in Figure 1), (3) the exposure variable is significantly associated to the outcome (i.e., c path, total effect of X on Y is significant, Figure 1), and (4) the significant relation between the exposure and outcome (direct effect, c' path) is no longer significant when controlling for mediator (indirect effect, a x b), with the strongest demonstration of mediation occurring when the path from the independent variable to the outcome variable is zero. While requirements (1) and (2) have been accepted as correct criteria to identify a potential mediator, requirements (3) and (4) have been critiqued by many scholars (25) because the effect of X on Y may not be significant when direct and mediated effects have opposite sign (inconsistent mediation) and because mediation can be partial or complete. When mediation is complete, after controlling for M, the direct path from X to Y would be zero. When mediation is partial, the path from X to Y can still be significant, but the effect should be reduced if mediation is indeed present.

There are several software programs available for the estimation of causal mediation effects in single mediator model including SAS CAUSALMED procedure, the mediation R package, as well as macros such as Valeri and Vanderweele (2013) SAS (23,24) (see supplementary data for further programs).

Usually, mediation analysis requires the calculation of four coefficients, Figure 1:

1) the a-coefficient, the effect of the mediator on the independent variable;
2) the b-coefficient, the effect of the dependent variable on the mediator while controlling for the independent variable as a potential confounder;
3) the c-coefficient, the total effect of the independent variable on the dependent variable; and
4) the c'-coefficient, the direct effect of the independent variable on the dependent variable while controlling for the mediator.

The ab-coefficient (a*b) represents the mediation effect. Complete mediation is indicated when the ab-coefficient is significant, and the c'-coefficient is equal to 0. Partial mediation is indicated when the ab-coefficient is significant and c' is reduced (12). All these calculations can be done by fitting two regression models, the mediator model and then outcome models and the outputs from the mediator and outcome regression models served as the main inputs to estimate the causal effects for the single mediator model (23,28,32,33) (see supplementary data for further details).

4. METHODS

5.1 Data and study population

The participants of the present study were part of the Belgian Health interview Survey (BHIS) 2018. The BHIS is household survey organized every 4 to 5 years. Participants are selected through a stratified clustered multistage sampling design (34). The target population consists of all Belgian residents, including older people who live in nursing homes. In the BHIS, information is collected on the health status, health behavior including HL, health care consumption and sociodemographic characteristics and use of medicines of all participants.

The BHIS data were individually linked to the Belgian Compulsory Health Insurance (BCHI) data using the unique national register number (HISlink 2018). The BCHI data contain exhaustive and detailed information on the reimbursed health expenses of over 99% of the total population. The database also includes a limited amount of socio-demographic information. The BCHI data were provided by the Intermutualistic Agency (IMA). IMA is a joint venture of the seven national sickness funds and collects and manages all data on healthcare expenditures as well as prescription information on reimbursed medicines (Pharmanet data) (35). Pharmanet logs all data on reimbursed dispensed medication from public pharmacies in Belgium. Pharmanet data include information on the date of dispensing, the quantity per package (QPP), the daily defined dose (DDD) and the national code number of the medicine (CNK codes) which allows to link each medicine to its ATC-code. The list of ATC codes per CNK codes was provided by the NIHDI.

A total of 11611 individuals participated to the BHIS 2018, among those, 10933 were linked with BCHI data resulting with an overall linkage rate of 94%. In the BHIS, information on HL is only available for people aged 15 years and over, who responded them self (proxy interview are excluded). Therefore, in this study, only people aged 15 years and over with valid information on HL (n = 6878) are considered, Figure 2.

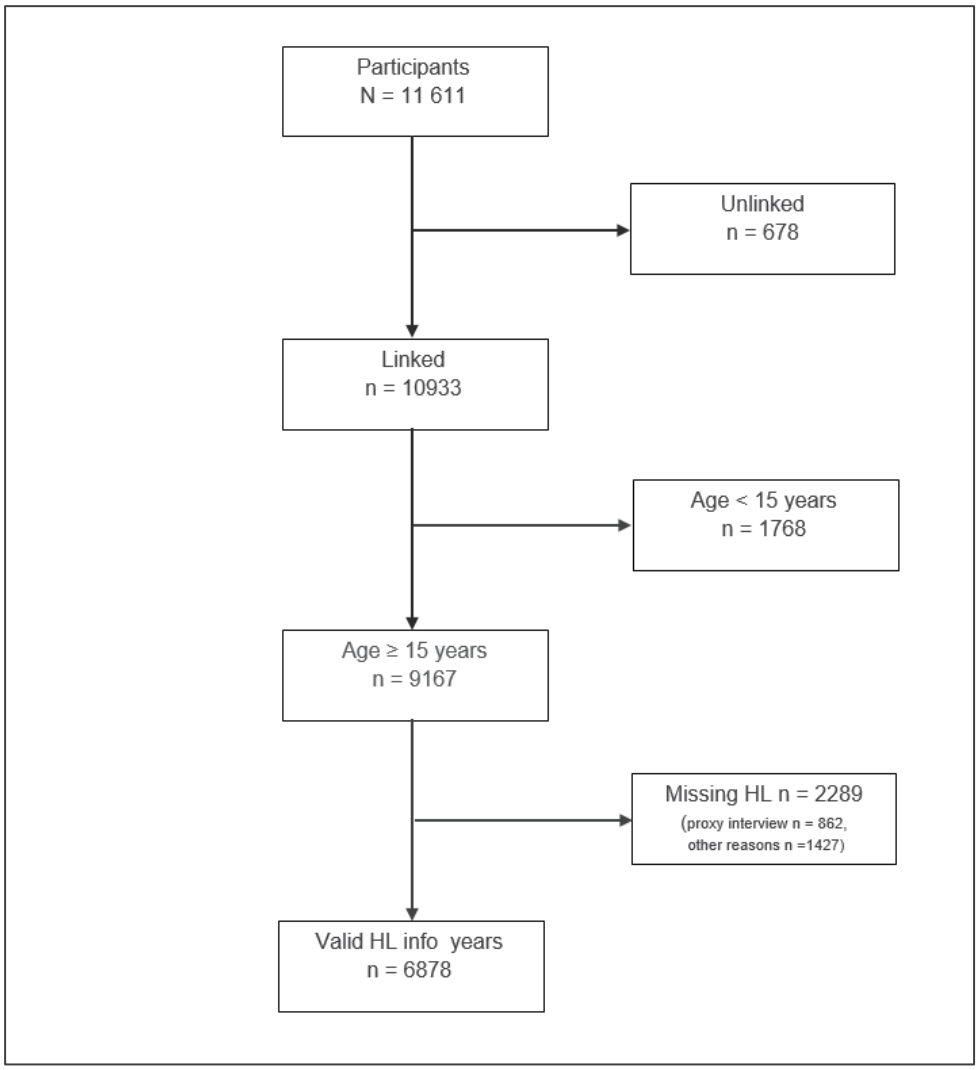

Figure 2: Participant selection process for analysis, HISlink 2018, Belgium

5.2 Measures

5.2.1 Dependent variables – Health(-related)outcomes

HRO were measured by selected health care indicators that were selected in consultation with NIDHI, namely preventive dental care use, breast cancer screening, vaccination against flu among older people, use of antibiotics, having a GMR and use of antidepressants. The information on these outcomes was retrieved from the BCHI data source.

Preventive dental care among adult population aged 18 years and over

The selected indicator is the proportion of the adult population aged 18 years and over who had at least one contact with a dentist in the reference period, i.e. in 2018, for preventive care such as an oral examination, a prophylactic cleaning, scaling, etc. The specific NIHDI nomenclature codes for the preventive dental care can be found in (36). Only adults aged 18 years and over are considered for this indicator.

Global medical record among population aged 15 years and over

This outcome relates to the percentage of the population aged 15 years and over who had a GMR in 2018. The indicator is constructed based on NIHDI specific nomenclature codes related to having either a GMR, an electronic GMR, or a lump sum GMR "forfait GMR" for at least six months (35), see Table S1 in supplementary files.

Use of antibiotics among population aged 15 years and over

This indicator is defined as the proportion of the population aged 15 years and over with at least one prescription of an antibiotic between 01/07/2018 and 30/06/2019. Pharmanet data were used to identify cases of use of antibiotics. Antibiotic use was defined as having obtained at least one prescription of a medicine belonging to ATC-code group J01 (antibacterials for systemic use) from a public pharmacy (see Table S1 in supplementary data) As antibiotic use has probably a seasonal pattern, there may be more than one peak in antibiotics use in a calendar year. Therefore in order to include only one winter peak per 12-month period, instead of the months January to December, we used the period from July 01, 2018 to June 30, 2018 to express the annual antibiotic use data (37).

Vaccination against flu among a community dwelling older people aged 65 years and over

This indicator expresses the proportion of the population aged 65 years and over that is vaccinated against influenza in the reference period, i.e., calendar year 2018. Older people aged 65 years and over residing in an institution were excluded in the IMA data, because in the BCHI data only vaccines which have been reimbursed are taken into account (38). All vaccines belonging to the ATC 4 class J07BB (anti-influenza vaccines) were considered.

Use of antidepressants among adult population aged 18 years and over

Percentage of adults aged 18 years and over with at least one prescription of an antidepressant (38) (ATC code=N06A) in 2018. Moreover, an indicator based on the yearly threshold of at 90 DDD was also calculated and used in sensitivity analysis.

Mammography among women aged 50-69 year in 2018

Proportion of women aged 50-69 having received at least one mammogram within the last two years, i.e., within the reference year or the reference year-1. In the BCHI data source, the mammographies realized within the screening program follow a specific procedure, and have their own billing codes. However, these codes do not allow to sufficiently discriminate screening within the program from the other mammographies (opportunistic screening, diagnostic evaluation). Therefore, in this study, all mammograms are considered, within or outside the context of the organised screening programme and we assumed that the largest part of the mammographies undergone between 50 and 69 is made for screening purposes, and therefore we used this information as a proxy of the breast cancer screening. The NIHDI nomenclature codes used can be found in Table S1 in supplementary files.

5.2.2 Independent variables

Information on independent variables was included from the BHIS. For the purpose of the present study, educational attainment and household income were utilized as proxy indicators

of the SES. In the present study we focused on educational attainment and income as independent variables because they are the frequently used indicators of SES from previous studies (8,9,12,13,39). Other indicators such as occupation (9,39) and race/ethnicity (8,13) are also used, but were not considered here.

Educational attainment is based on the highest level of education achieved in the household. Possible values are “primary or no degree”, “secondary inferior”, “secondary superior”, and “superior education” following the ISCED-11 classification, whereby superior education includes all obtained degrees higher than secondary superior (40). These values are recorded into two categories for the analyses: lower secondary’s degree or lower (“primary or no degree”, “secondary inferior”) and higher secondary’s degree or higher (“secondary superior”, and “superior education”). For income level, the quintiles of the equivalent household income were recoded in low (quintile 1–3) and high (quintile 4 and 5).

5.2.3 Mediator variable

The HL level of the Belgian population was assessed through the Belgian BHIS in 2018, using the 6-items European Health Literacy Survey Questionnaire (HLS-EU-Q6), which is a short-short form of the original 47-items tool (HLS-EU-Q47) (41). Like the original, the HLS-EU-Q6 is a self-reported tool whereby participants are asked how easy or difficult they find it to perform an information-related task, using Likert-type responses (“very easy” = 4; “fairly easy” = 3; “fairly difficult” = 2; “very difficult” = 1. “Don’t know” or refusal were recoded as missing. The scale final score measuring HL is the mean value on the six items, which varies between 1 and 4. Only respondents who answered at least 5 items were considered. Based on the final score, three possible levels of HL are defined: insufficient level of HL ($1 \leq x \leq 2$); limited level of HL ($2 < x < 3$); sufficient level of HL ($3 \leq x \leq 4$). In this study, HL was treated as a dichotomous variable grouping together insufficient and limited levels (Insufficient/limited level of HL / Sufficient level of HL).

5.2.4 Confounding variables

Based on previous studies, demographic characteristics that were identified as potential confounders in this study were sex (male/female) and age (in years as a continuous variable) (9,10,12,39). Finally, in a sensitivity analysis, the models for the use of antidepressants were adjusted further for psychological distress (Yes / No).

5.3 Statistical analysis

Descriptive analysis

Descriptive statistics were presented summarizing the sociodemographic characteristics of the participants. Indicators were presented as a percentage in case of categorical variables and a mean in case of continuous variables. Participants characteristics were estimated overall and by level of HL. Comparisons were statistically tested using a $\chi 2$ test for categorical variables and a t-test for normally distributed continuous age variable. Correlation analyses were performed to determine the relationships between the main variables, i.e., the independent variables, the outcomes variables and the mediator variable (10–12,42,43) prior to mediation analysis. Table 1 provides the guidance of correlation coefficient interpretation (44).

Table 1: Guidance of correlation coefficient interpretation

Absolute Magnitude of the Observed Correlation Coefficient	Interpretation
0.00-0.10	Negligible correlation
0.10-0.39	Weak correlation
0.40-0.69	Moderate correlation
0.70-0.89	Strong correlation
0.90-1.00	Very strong correlation

Mediation analysis

To test the hypothesis that HL is a pathway by which educational attainment and household income affect the selected health outcomes, we examined the mediation effect of HL separately for each of the two SES factors considered (9) and for each of the selected health care outcome. Moreover, in additional analysis, we also performed a mediation analysis to assess the mediation effect of HL in the relationship between both SES variables and two additional health outcomes that are expected to required more individuals involvement and decision, i.e., physical activity and nutritional habits.

The analysis was done in two steps as mentioned above. Separate mediation models were applied for all the indicators of health outcomes on the basis of logistics regression analyses. All logistics regression analyses were controlled for age, sex, and region of residence as covariates, because they were expected to be all related to the key variables (see Figure 3 for the conceptual model). In the analyses, age was entered as a continuous variable, HL and SES variables were used as dichotomous (9), whereas region of residence was included as categorical variable with 3 levels. In addition, the outcome model also contained an interaction term for the independent variables x the mediator. By including an interaction term, we assume that the odds ratio (OR) comparing categories of SES differs according to the mediator variable, i.e., HL, and vice versa. The interaction term gives multiplicative effect of non-reference levels of the two categorical variables. For nominal by nominal interactions, we examine the effects of two covariates simultaneously by multiplying the odds ratios. For example, to see the effect of two categorical covariates x1 and x2, we multiply $e^{\beta x1}$ with $e^{\beta x2}$ to get $e^{\beta x1}e^{\beta x2} = e^{\beta x1 + x\beta x2}$. Note that we can either a) first add the coefficients and then exponentiate, or b) first exponentiate to get odds ratios, and then multiply.). So, with interaction, we calculate the OR as follows: $OR_{x1,\,x2} = e^{\beta x1}e^{\beta x2}e^{\beta x1x2}$ (45,46).

All analyses were performed using SAS® (version 9.4), taking into account the survey weights for the descriptive analysis. The Causalmed procedure was used for the mediation analysis (23,33).No survey weights were included in the mediation analysis because the SAS Causalmed procedure did not support the complex survey settings. Proc Causalmed computes the TE of the exposure on the outcome and decomposes it into an indirect effect (NIE) and a direct effect (NDE). The TE, NIE and NDE outputs are produced on the risk difference scale or on OR scale. In terms of interpretation, the indirect effect reflects the magnitude of the effect that is transmitted through the mediator, whereas the direct effect accounts for all the other possible causal chains. In addition, the Proc Causalmed yields the proportion mediated (PM), which should be interpreted as an estimate of the percentage of the total effect that is exerted through the mediator (12,23,33,39) and provide insight into the relative importance of the mediating role of health literacy. Missing values were excluded from the analyses. For each analysis, an α level below 0.05 was considered as significant. All P values are two-tailed.

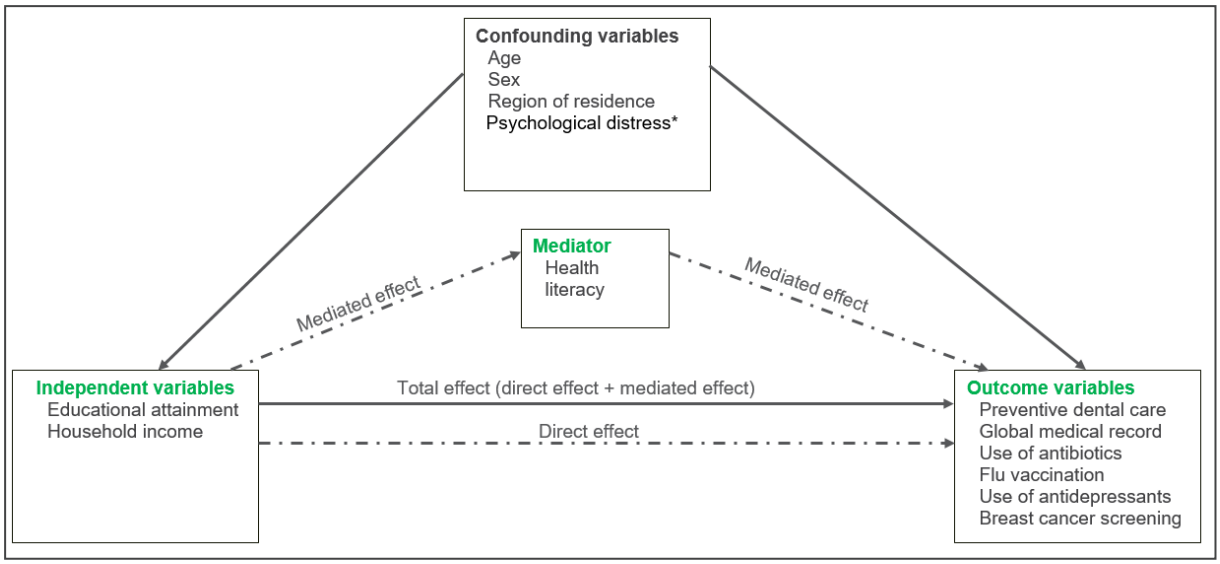

Figure 3: Conceptual model of HL as a mediator of the association between SES factors and Health care outcomes. **Psychological distress was use as confounding variable for the use of antidepressants only in sensitivity analysis*

5. RESULTS

1.1 Descriptive statistics of the sample

Participants characteristics

Participants characteristics are presented in Table 2. The crude *n* are presented but all percentages are weighted to match the distribution of the population in terms of age, sex and region of residence. Females represented 52% of the population and the mean age is 48 years old (SD = 0.4). More than eight participants out of ten completed higher secondary's degree or higher (84%). As for income, 56% of the participants belonged to a household with higher income category. In terms of HL, sufficient level of HL was found in 66.5% of the population. People who had a sufficient level of HL were more likely to be male, higher educated, and belong to high household income category. Further characteristics can be found in Table 2.

Table 2: Participants characteristics overall and by level of health literacy, n = 6878, HISlink 2018, Belgium

	Total n (% for column)	Health Literacy (HL) levels n (% for raw)		P value
		Sufficient level of HL	Insufficient/limited level of HL	
All	6878 (100)	4532 (66.5)	2346 (33.5)	
Gender				*0.0141*
Male	3255 (48.3)	2182 (68.4)	1073 (31.6)	
Female	3623 (51.7)	2350 (64.8)	1273 (35.2)	
Age, mean ± SE	48.2 ± 0.4	48.2 ± 0.4	48.1 ± 0.6	
Educational attainment				
Lower secondary's degree or lower	1160 (15.7)	599 (51.4)	561 (48.6)	<0.0001
Higher secondary's degree or higher	5610 (83.2)	3862 (69.3)	1748 (30.7)	
Missing	108 (1.1)	71 (69.0)	37 (40.0)	
Household income				<0.0001
Lower household income	2812 (38.3)	1739 (61.5)	1073 (38.5)	
Higher household income	3130 (49.4)	2171 (69.9)	959 (30.1)	
Missing	936 (12.3)	622 (68.8)	314 (31.2)	
Psychological distress				<0.0001
Yes	2260 (32.6)	1209 (53.7)	1051 (46.3)	
No	4501 (65.9)	3242 (72.8)	1259 (27.2)	
Missing	117 (1.5)	81 (71.5)	36 (28.5)	

Prevalence of health (-related) outcomes

The prevalence rates of the selected HRO overall and by level of HL are presented in Figure 4. 40.0% of the adult population aged 18 years and over had a preventive dental care consultation in 2018. The prevalence was significantly higher among individuals with sufficient level of HL as compared to those with insufficient/limited level of HL (41.4% vs. 37.2%, p = 0.0152). 78.5% of the population aged 15 years and over were found to have a GMR. This

prevalence was not significantly different between individuals with sufficient level of HL and those with insufficient/limited level of HL (78.2% vs. 79.2%, p = 0.4983).

As far as use of antibiotics is concerned, 35.8% of the population aged 15 years and over had used at least once an antibiotic in the reference period. This proportion was slightly higher (but not significantly) among individuals with insufficient/limited level of HL compared to those with sufficient level of HL (37.1% vs. 35.1%, p = 0.2261). Among older population aged 65 years and over, 55.8% were vaccinated against flu. This proportion was significantly lower in individuals with sufficient level of HL (53.0%) and reached 60.7% in those with insufficient/limited level of HL (p =0.0278). Of the adult population aged 18 years and over, 13.0% had used at least once an antidepressant in the reference period. There was a significant difference in the use of antidepressants among individuals with sufficient level of HL (10.8%) and those with insufficient/limited level of HL (16.8%), p <.0001. Finally, 66.1% of women aged 50-69 years had undergone breast cancer screening in the past two years. There was no significant difference among women with sufficient level of HL (66.5%) and those with insufficient/limited level of HL (65.1%), p = 0.7095.

The prevalence of HRO varied significantly by educational attainment. Low educated people had a lower likelihood of having received preventive dental care compared to higher educated people (20.2% vs. 43.6%), participated less in breast cancer screening (52.5% vs.69.2%), but presented with a higher probability of having a GMR (82.6% vs. 77.8%), using antibiotics (41.6% vs. 34.7%), having been vaccinated against flu (57.3% vs. 55.1, difference not significant), and using antidepressants (18.3% vs. 11.7%), Figure 5.

The prevalence of HRO also varied by level of household income. While persons belonging to a household with a low income category had a lower probability of having received preventive dental care (32.0% vs. 45.3%) and breast cancer screening (57.9% vs. 74.3%) as compared to those belonging to higher household income category, they had a higher probability of having a GMR (80.4% vs.77.2%), using antibiotics (36.8% vs 35.1%), having been vaccinated against flu (57.1% vs. 55.5%, difference not significant), and using antidepressants (17.3% vs.9.5%), Figure 6.

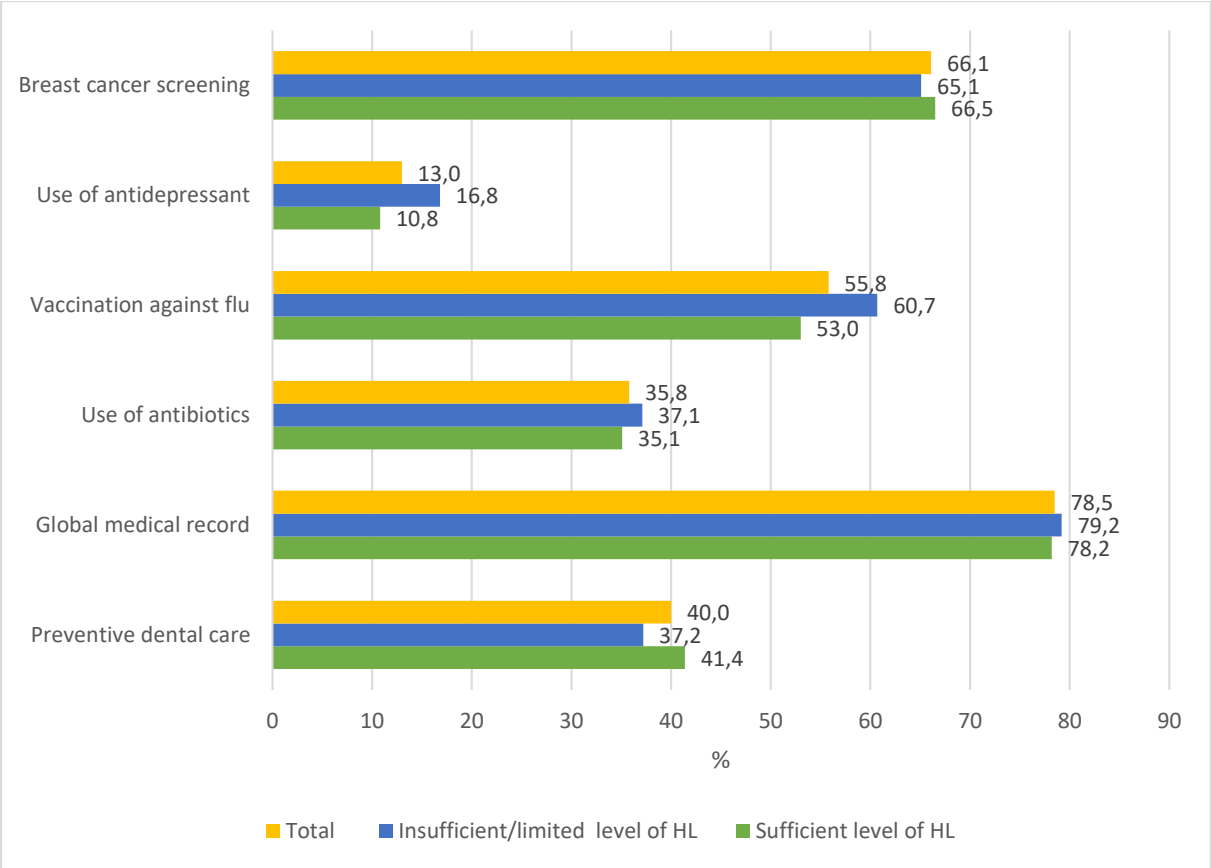

Figure 4: Prevalence of health care outcomes overall and by HL level, HISlink 2018, Belgium

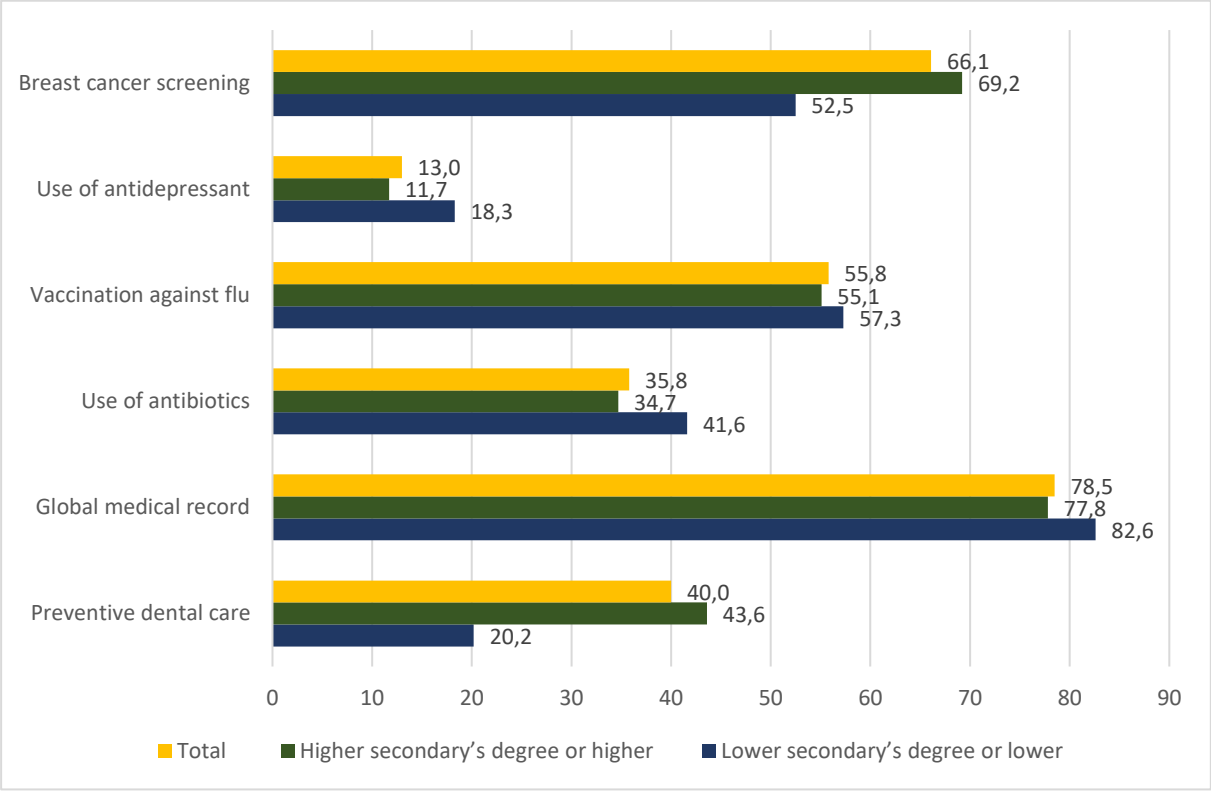

Figure 5: Prevalence of health care outcomes overall and by educational attainment

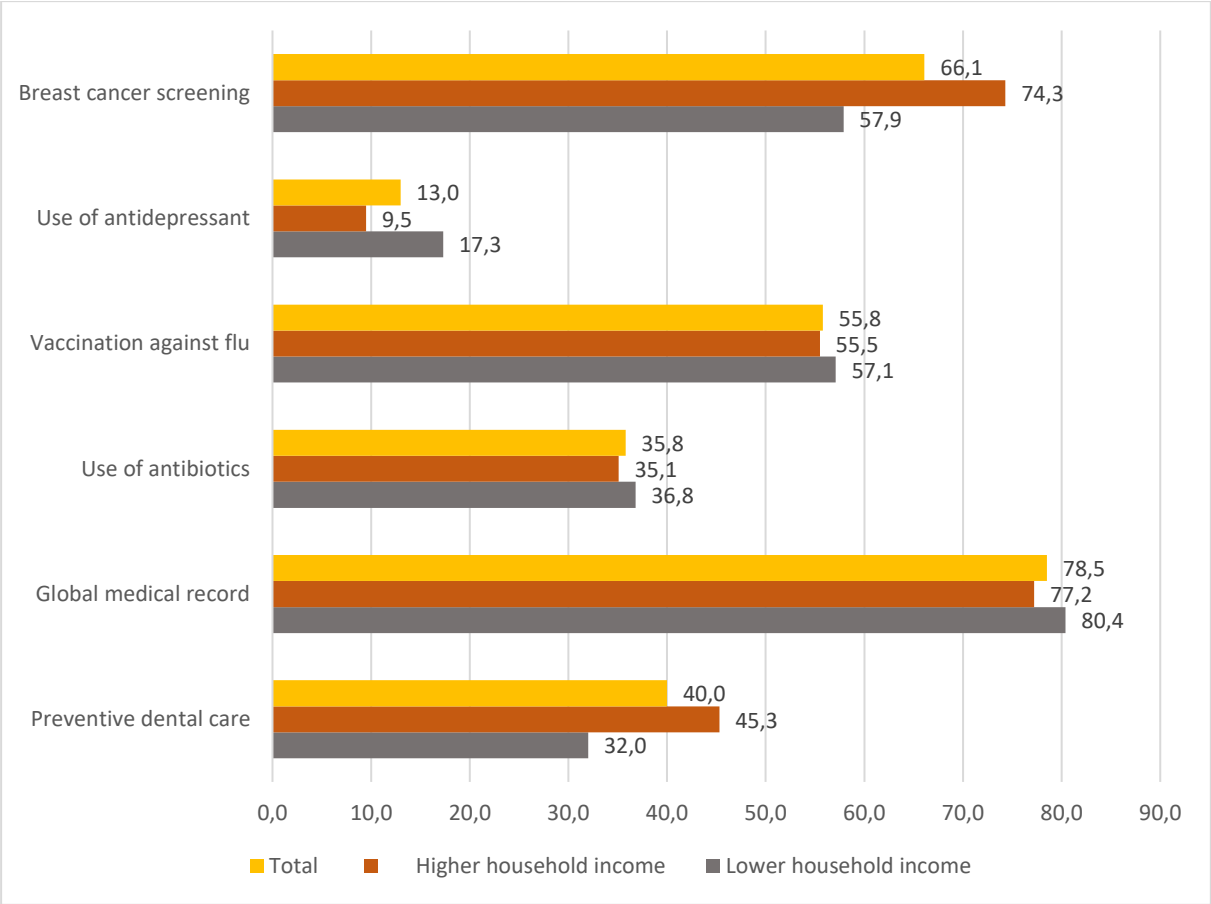

Figure 6: Prevalence of health care outcomes overall and by household income level

1.2 Association between health literacy, educational attainment, household income and health(-related) outcomes

Overall, there is a positive weak correlation between HL and SES variables ($r = 0.250$, $p < 0.0001$ and $r = 0.130$, $p < 0.0001$ for educational attainment and higher household income, respectively), indicating that higher educational attainment and higher household income are associated with having a sufficient level of HL. Similar results are found for health care use variables (see Table S3 in supplementary data). The positive association between educational attainment, household income and HL is confirmed in the regression analysis (mediator model, see Table S4 in supplementary files).

In line with the findings in Figures 5 and 6, a positive weak correlation was observed between educational attainment, household income and preventive dental care and breast cancer screening, in the way that higher educational attainment and higher household income were associated with higher likelihood of receiving preventive dental care and breast cancer screening (Table 3). However, after correction for participants characteristics, the association of educational attainment with breast cancer screening was no longer significant (see Table S5 -Outcome model in supplementary files).

On the other hand, a negative negligible to weak correlation was found between the SES variables and GMR, use of antibiotics, vaccination against flu and use of antidepressants. This negative correlation suggests that a lower SES is related to a higher likelihood of having a GMR, use antibiotics, get vaccinated against flu and use antidepressants, as shown in Figure 5 and 6. After adjustment for participants characteristics, only the association between GMR and educational attainment and those between use of antidepressants and household income remain significant (see Table S5 - Outcome models in supplementary files).

As shown in Figure 3 above, HL was positively correlated with preventive dental care (r = 0.054, p =0.0074), indicating that sufficient level of HL was related to higher preventive dental care use. In contrast, HL was negatively correlated with flu vaccination (r = −0.101, p =0.0133) and with use of antidepressants (r = −0.151, p <0.0001), indicating that lowest level of HL was associated with a higher likelihood of getting vaccinated against flu and with a higher use of antidepressants. No significant correlation was observed between HL and GMR, use of antibiotics and participation in breast cancer screening (Table 3). In general, these findings are confirmed in the regression analysis (see Table S5 - Outcome models in supplementary files).

Table 3: Correlation between health literacy, educational attainment, household income and health(-related) outcomes

	Preventive dental care (n=6682)	Global medical record (n=6878)	Use of antibiotics (n = 6878)	Vaccination against flu (n =1540)	Use of antidepressants (n = 6682)	Breast cancer screening (n = 1261)
Health literacy	0.054**	-0.029	-0.036	-0.101**	-0.151***	0.047
Education	0.318**	-0.147***	-0.073**	-0.066	-0.119***	0.231***
Income	0.232**	-0.060**	-0.050**	-0.024	-0.207***	0.251***

*** P < 0.05; ***P < 0.0001; All P values are two-tailed*

1.3 Mediation effects of health literacy

Table 4 presents the mediation effects of HL in the association between health care use and both SES variables.

Mediation effects of HL on the relationship between educational attainment and health (-related) outcomes

HL was found to significantly mediate the associations between educational attainment and preventive dental care, (OR of NIE = 0.94, 95% CI: 0.89-0.99), and between educational attainment and use of antidepressants (OR of NIE = 1.08, 95% CI: 1.01-1.14). The percentage mediated is about 4% for preventive dental care and not significant for the use of antidepressants. No mediating effects of HL was found in the relationship between educational attainment and the other HRO.

Mediation effects of HL in the relationship between household income and health (-related) outcomes

HL significantly mediates the association between household income and preventive dental care, (OR of NIE = 0.98, 95% CI: 0.97-0.99), and between household income and use of antidepressants (OR of NIE = 1.04, 95% CI: 1.02-1.06). The percentage mediated is about 3% for preventive dental care and 10% for the use of antidepressants. The mediating role of HL was not significant in the relationship between household income and the other HRO

Table 4: Mediation effects of health literacy in the relationship between health(-related) outcomes and socioeconomic status (educational attainment and household income)

	Odds Ratio[a] (95% CI)	
	Educational attainment[b]	**Household income[c]**
Preventive dental visit vs. No preventive dental visit		
Total Effect (TE)	0.40 (0.34-0.46)***	0.57 (0.51-0.63)***
Natural direct effect (NDE)	0.43 (0.36-0.50)***	0.58 (0.52-0.65)***
Natural indirect effect (NIE)	0.94 (0.89-0.99)**	0.98 (0.97-0.99)**
Percentage mediated (%)	**4.4 (0.67 to 8.1)****	**2.5 (0.5 to 4.6)****
Global medical record vs. No Global medical record		
Total Effect (TE)	1.28 (1.06-1.50)**	0.98 (0.85-1.10)
Natural direct effect (NDE)	1.28 (1.05-1.51)**	0.97 (0.84-1.09)
Natural indirect effect (NIE)	1.00 (0.94-1.06)	1.01 (1.00-1.03)
Percentage mediated (%)	**0.16 (-26.7 to 27.1)**	**-64.4 (-470.5 to 341.6)**
Use of antibiotics vs. No use of antibiotics		
Total Effect (TE)	1.15 (0.99-1.30)	1.06 (0.94-1.17)
Natural direct effect (NDE)	1.12 (0.96-1.27)	1.05 (0.93-1.16)
Natural indirect effect (NIE)	1.03 (0.98-1.07)	1.01 (1.00-1.02)
Percentage mediated (%)	**19.7 (-18.1 to 57.6)**	**18.6 (-22.8 to 59.9)**
Vaccination against flu vs. No vaccination against flu		
Total Effect (TE)	0.96 (0.75-1.19)	0.85 (0.64-1.07)
Natural direct effect (NDE)	0.99 (0.75-1.24)	0.86 (0.64-1.08)
Natural indirect effect (NIE)	0.98 (0.90-1.06)	0.99 (0.96-1.03)
Percentage mediated (%)	**91.0 (-827.1 to 1009)**	**2.9 (-17.8 to 23.5)**
Use of antidepressants vs. No use of antidepressants		
Total Effect (TE)	1.12 (0.91-1.32)	1.57 (1.32-1.83)***
Natural direct effect (NDE)	1.04 (0.84-1.24)	1.51 (1.27-1.76)***
Natural indirect effect (NIE)	1.08 (1.01-1.14)**	1.04 (1.02-1.06)**
Percentage mediated (%)	**66.9 (-47.7 to 181.5)**	**10.4 (4.2 to 16.0)****
Breast cancer screening vs. No breast cancer screening		
Total Effect (TE)	0.53 (0.38-0.69)***	0.52 (0.39-0.65)***
Natural direct effect (NDE)	0.55 (0.38-0.72)***	0.52 (0.39-0.66)***
Natural indirect effect (NIE)	0.96 (0.90-1.03)	1.00 (0.96-1.02)
Percentage mediated (%)	**4.1 (-4.0 to 12.2)**	**0.7 (-2.7 to 4.1)**

*[a] Adjusted by age and gender; ** p < 0.05; *** p < 0.0001. [b] Because of missing value in this variable, the final n in the model were 6575 for preventive dental care and use of antidepressants; 6770 for global medical record and use of antibiotics; 1513 for flu vaccination and 1235 for breast cancer screening. [c] Due to the missing value in this variable, the final n in the model were 5781 for preventive dental care and use of antidepressants; 5942 for global medical record and use of antibiotics; 1338 for flu vaccination and 1068 for breast cancer screening.*

Additional analysis

In additional analysis, we performed a mediation analysis to assess the mediating effects of HL in the relationship between SES variables and HRO that are expected to required more individual involvement and decision, i.e., physical activity and eating habits. A mediation effects of HL was found in the relationship between both educational attainment and household income with physical activity (defined as 'Spend at least 150 minutes per week in physical activities of at least moderate intensity'), Table S6 in supplementary data, and nutritional habits (defined as 'Eating at least 5 portions fruits and vegetables daily'), Table S7 in supplementary data. More specifically, individuals with low educational attainment and low household income are less likely to be physically active and the mediating effects of HL account for 7% and 12% respectively. Similarly, individuals with low SES have a lower probability to have healthy eating habits. The mediating effects of HL account for 12% in the relationship with educational attainment and reaches 17% in those with household income.

6. CONCLUSIONS AND RECOMMENDATIONS

The reduction of health inequities is an important objective for public health policies. It is therefore important to identify factors that could help to achieve this goal. Among the individual factors, SES and HL are of great interest as they are related to equity and health inequalities. In contrast to a number of SES factors that are more difficult to modify, HL is a more easily modifiable factor (13,39). This exploratory study examined the relationship between SES as measured by educational attainment and household income, HL, and HRO that were of great interest from public health perspective. It also explored if HL acts as a mediator in this association.

Overall, HL was found to be positively associated with both SES variables. The associations between SES and HRO vary across the outcomes in terms of direction and magnitude. A low SES was associated with a lower probability of using preventive dental care, and a lower probability of undergoing breast cancer screening, and with a higher probability of having a GMR, using antibiotics, and using antidepressants. There was not significant association between SES variables and vaccination against flu. Similarly, the associations between HL and HRO also vary. Lower HL is associated with lower probability of using preventive dental care, and with a higher probability of using antidepressants and of being vaccinated against flu. The association between HL and vaccination against flu could be partly explained by the fact that individuals with a lower HL may belong to a risk group and are more likely to have contact with physicians and as such be offered an influenza vaccination. No significant association was found with the other health care usage variables.

Regarding the mediating role of HL in the relationship between SES factors and HRO, the findings showed that HL may constitute a possible pathway by which SES variables influence preventive dental care and use of antidepressants, suggesting that strategies for improving preventive dental care or reducing the use of antidepressants may benefit from considering the peoples' level of HL. The low percentage mediated for the use of antidepressants might suggest a shared decision between physician and patients.

Our results did not show that HL had a significant mediating contribution in the pathway through which SES determinants affect having GMR, use of antibiotics, vaccination against flu and participation in breast cancer screening. The findings for having a GMR and use of antibiotics are not surprising, as these are more related to physician decisions than to personal decisions affected by the individual's HL level. Also, in the descriptive analysis no significant correlation was found between HL and having GMR or use of antibiotics (Table 3). The findings with respect to vaccination against flu could be linked to the universal health care system that is in place in Belgium. Indeed, as suggested by previous studies (39,47), in countries with universal, publicly-funded health care systems, as is the case of Italy, the burden exerted by SES on influenza vaccination uptake is small or absent, since it is reduced by an equitable access, free of charge, for all the categories provided by law. In Belgium, access to vaccination against flu among older population is free of charge. As individual decision are not likely to play a crucial

role in this behaviour, the influence of HL is minimal because. In this way, our findings for vaccination against flu among older population are in line with those in Zanobini et al. (2022), who also found that individuals with low SES were more likely to be vaccinated against flu and that HL did not mediate the relationship of any of the independent variables with influenza vaccination status (39).

With regard to breast cancer screening, we found a lower coverage among the low SES group but we did not find evidence that HL serves as a pathway by which education attainment or household income affect participation in breast cancer screening, probably indicating a possible influence of the universal health coverage in place. This result is not surprising as the condition 2 for considering HL as a mediator was not met. Indeed, as shown in Table 3 and Table S5 in the supplementary files, there was no significant association between HL and breast cancer screening. In the literature, the results of studies exploring the mediation effect of HL in preventive care such as cancer screening are inconsistent (8). While Bennett et al. (2009) found that HL mediated the relationship between education and undergoing mammography (48), Richie et al. (2022) found no significant mediating effect of HL in predicting intention to screen among women in five EU countries (49).

As expected, the strongest mediation effects of HL were found in the association between educational attainment and household income with health related behaviours that require an individual decision, such as physical activity and nutritional habits (Table S6 and S7 in supplementary files). Our results are in line with the finding in the literature (11).

This study has a number of limitations that must be acknowledged. First, we used at least one use of antibiotics and antidepressants in the reference period to identify related cases. It is possible that individuals who have few reimbursed antidepressants do not actually suffer from depression. Moreover, we did not adjust our final model for depression. To take this into account, we performed two sensitivity analyses. In the first, a threshold of 90 DDD per year of specific medication ATC codes was used to identify cases; in the second, the model was corrected for psychological distress. We found that even taking into account a threshold of 90 DDD, the mediating effect of HL in the relationship between household income and use of antidepressants remains significant (OR = 1.04, 95% CI: 1.02-1.07). The percentage mediated was about 13% (see Table S8 in supplementary data). In the second sensitivity analysis, when adjusting for psychological distress, only a trend of mediation of HL on the association between household income and use of antidepressants was observed (OR = 1.02, 95% CI: 1.00-1.03; p = 0.0660), with the effect accounting for around 6% of the total effect (see Table S9 in supplementary data).

A second limitation is that no distinction could be made between mammographies as part of a screening program and opportunistic mammographies. This is because nor BHIS nor BCHI allows to clearly disentangle both type of mammographies. The actual indicator that was assessed in the BHIS was “having had a mammography”, including both screening and opportunistic mammographies. In the BCHI data source, the mammographies realized within the program follow a specific procedure, with their own billing codes, yet these codes do not allow to sufficiently discriminate screening within the program from the other mammographies (opportunistic screening, diagnostic evaluation). In this study, we assumed that the largest part of the mammographies undergone between 50 and 69 is made for screening purposes, and therefore we used this information as a proxy of the breast cancer screening.

Thirdly, the higher number of missing HL values (25% missing values) and the use of complete case analysis may have affected the final results. It will be interesting in future analyses to assess the impact of these missing values in a sensitivity analysis using multiple imputation for example. In addition, some of the 95% confidence intervals for the PM in Table 4 are fairly wide and span from negative to positive values (e.g., vaccination against flu among older people). This indicates that the corresponding point estimates might not be very accurate. More data would yield a more precise interval estimate.

Fourthly, the instrument that was used to assess HL in this study was a generic one, which may explain the relatively low percentage of mediated effects for HL. In fact, some authors suggest the use of health outcome-specific literacy instrument (e.g., vaccine literacy) for more adequate assessment of HL (39). Moreover, the short 6-item form of the HLS-EU questionnaire that was used in the BHIS 2018 may not have captured the level of HL sufficiently well. While the use of the short form was warranted because the already substantial length of the BHIS precluded the use of a longer form of the HL questionnaire, for the next BHIS survey 2023, a revised 12-item version of the questionnaire will be used, which has better validity. This will allow to confirm the results of this exploratory analysis on the BHIS 2023 data, and consider additional factors that were not taken into account in this study, but which could act as mediators in the pathways through which SES influences health care use and outcomes. Future studies could also take other potential mediators into account of the relationship by which SES factors influence health outcomes, such as health behaviours and lifestyles, social and environmental exposures, and consider the role of HL as a mediator in a broader framework (9,50,51). Zanobini et al. (2022) also suggest for future research to investigate the hypothesis that SES could be the mediator variable between HL and influenza vaccine uptake (39).

Finally, due to the lack of data in the HISlink and also because of the small sample, it was not possible to perform the mediation analysis for appropriate follow-up of diabetic patients.

To conclude, this study provides evidence that HL serves as a pathway by which educational attainment and household income affect preventive dental care and use of antidepressants. Although the influence of HL in this pathway is rather limited, the findings suggest that strategies for improving preventive dental care or reducing use of antidepressants may benefit from considering the patients' level of HL. There was no significant mediating contribution of HL in the pathway by which SES affects having a GMR, use of antibiotics, vaccination against flu and breast cancer screening. Further data and analysis are needed to confirm our results and to better explore the mediating effects of HL in other domains such as lifestyle, health status, and health care use.

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8. ANNEX

Supplementary file

1. Technical aspects to mediation analysis

1.1. Estimation approaches and conditions for mediation analysis

Overall, two approaches are used in mediation analysis, the traditional regression approach and the counterfactual approach (1). The classic regression approach to mediation analysis has been largely used in psychology and in the social sciences and has been strongly influenced by the work of Baron and Kenny (2). The causal diagram in Figure 1 captures how those authors conceptualized the role of a mediator variable. In this figure, which represents a simple mediation model, X denotes an exposure (or treatment) variable, M denotes the mediator and Y denotes the outcome variable (1). However, this traditional approach has important limitations. First, it lacks a general framework to define causal mediation and related effects. The causal effects are not well defined when binary mediators or outcomes are considered. Second, it does not take into account the interaction effect between treatment and mediator. Third, it does not explain the assumptions and identification conditions for valid causal effect estimation (1,3). More recently, new advances in mediation analysis have been made by using the counterfactual framework. The counterfactual approach to mediation analysis (causal mediation) (4) offers solutions to the limitations of traditional approach mentioned above (1). Within this framework, direct and indirect effects are well defined in terms of counterfactual outcomes (4–6). Furthermore, whereas traditional mediation analysis emphasizes more about the decomposition of the TE in NDE and NIE, the controlled direct effect (CDE) and the percentage eliminated (PE) are more useful constructs from a policy-making or intervention perspective (3):

Total effect (TE)

The total effect (TE) for a subject is defined as the difference between the counterfactual outcomes at the treatment and control levels.

Naturel direct effect (NDE)

The natural direct effect (NDE) for a subject is defined as the difference between the counterfactual outcomes at the two treatment levels when an intervention sets the mediator value to M = M0, which is the natural level of the mediator when there is no treatment.

Naturel indirect effect (NIE)

The natural indirect effect (NIE) for a subject is defined as the difference between the counterfactual outcomes at the two mediator levels at M1 and M0 when an intervention sets the treatment to T = 1.

Percentage mediated (PM)

The PM is the percentage of total effect that is mediated.

Controlled direct effect (CDE)

The controlled direct effect (CDE) for a subject is defined as the difference between the counterfactual outcomes at the two treatment levels when an intervention sets the mediator to a particular level, M = m. in other words, the CDE is the effect of independent variable if there is an intervention such that everyone in the population of interest has his or her mediator variable (HL) fixed to a specific level. By default, the sample mean of the mediator (if continuous variable) or its reference level (in case of binary variable) is used as the intervention level

Percentage eliminated (PE)

The PE is the portion of the TE that is eliminated when an intervention sets the mediator variable to a particular level.

The mediation effect analysis needs to meet the following conditions (1,7,8): (1) the exposure variable is significantly associated to the mediator (i.e., a path, from X to M in Figure 1), (2) there is a significant relationship between the mediator and the outcome (i.e., b path, from M to Y in Figure 1), (3) the exposure variable is significantly associated to the outcome (i.e., c path, total effect of X on Y is significant, Figure 1), and (4) the significant relation between the exposure and outcome (direct effect, c' path) is no longer significant when controlling for mediator (indirect effect, a x b), with the strongest demonstration of mediation occurring when the path from the independent variable to the outcome variable is zero. However, while requirements (1) and (2) have been accepted as correct criteria to identify a potential mediator, requirement (3) has been critiqued by many scholars (8). Consensus has been reached that the relationship between X and Y need not be statistically significant for M to be a mediator because the effect of X on Y may not be significant when direct and mediated effects have opposite sign (inconsistent mediation). Requirement (4) is also not necessary because mediation can be partial or complete. When mediation is complete, after controlling for M, the direct path from X to Y would be zero. When mediation is partial, the path from X to Y can still be significant, but the effect should be reduced if mediation is indeed present.

1.2. Steps in estimating mediation effects in single mediation model

There are several software programs available for the estimation of causal mediation effects in single mediator model: PROC CAUSALMED in SAS, the mediation R package, and the MedFlex R package, MODEL INDIRECT statement in Mplus, as well as macros such as Valeri and Vanderweele (2013) SAS and SPSS mediation macros, the Stata PARAMED macro, the Med4Way macro in Stata (9,10). Usually, mediation analysis requires the calculation of four coefficients: (1) regress the mediator on the independent variable (a-coefficient); (2) regress the dependent variable on the mediator while controlling for the independent variable as a potential confounder (b-coefficient); (3) calculate the total effect by regressing the dependent variable on the independent variable (c-coefficient); (4) calculate the direct effect by regressing the dependent variable on the independent variable while controlling for the mediator (c'-coefficient), Figure 1. The ab-coefficient (a*b) represents the mediation effect. Complete mediation is indicated when the ab-coefficient is significant, and the c'-coefficient is equal to 0. Partial mediation is indicated when the ab-coefficient is significant and c' is reduced (11). All these calculations can be done in two steps. First, two regression equations (linear in case of

continuous outcome and continuous mediator or logistic in case or binary outcome and binary mediator) were specified and fitted separately: the mediator model for the conditional distribution of the mediator given the independent variable, and the outcome model for the conditional distribution of the outcome given the independent variable and the mediator. The outcome model can be specify through model with only main effects from the treatment and mediator variables or through a model that includes both main effects and an interaction effect. In many studies it is unrealistic to assume that the exposure and mediator do not interact in their effects on the outcome. Carrying out mediation analysis incorrectly assuming no interaction may result in invalid inferences (1). Therefore, in general, without strong prior knowledge about the absence of the interaction effect, the latter type of model specification is recommended (3). Second, outputs of the mediator and outcome regression models served as the main inputs to estimate the causal effects for the single mediator model (1,6,9,12).

For example, in case of binary mediator and binary outcome, the mediator and outcome models can be written as follows:

Mediator model : Logit$\{P(M = 1|x,c)\} = \beta_0 + \beta_1 x + \beta'_2 c + e_1$ (Equation 1)

Outcome model : Logit$\{P(Y = 1|x,m,c,)\} = \theta_0 + \theta_1 x + \theta_2 m + \theta_3 xm + \theta'_4 c + e_2$ (Equation 2)

Where Equation 1 represents the effect of X on M (β_1 coefficient), Equation 2 represents the effect of X on Y adjusted for M (θ_1 coefficient), the effect of M on Y adjusted for X (θ_2 coefficient), and the effect of the XM interaction on Y (θ_3 coefficient). The magnitude of the θ_3 coefficient indicates how much the effect of X on Y (θ_1) varies across mediator levels (M) and how much the effect of M on Y (θ_2) varies across treatment levels (X). The θ_3 coefficient in Equation 2 approaches zero when there is no XM interaction. The β_0 and θ_0 terms in Equations 1 and 2 represent intercepts. The β'_2 and θ'_4 coefficient represent the effects of the baseline covariate (C) on the mediator and the outcome and the e_1 and e_2 terms represent residuals.

2. ATC – codes and nomenclature codes used in the cases definitions

Table S1 : ATC-codes / Nomenclature codes used for cases definition

Indicators	ATC-codes / Nomenclature codes
Global medical record	102771, 102793, 101371, 101393, 101312, 101334, 103574, 103596. Forfait GMR: 109616
Use of antibiotics	J01A, J01B, J01C, J01D, J01E, J01F, J01G, J01X, J01R, J01X.
Vaccination against flu	J07BB
Use of antidepressants	N06A
Mammography	450096, 450100, 450192, 450203, 461090, 461101.

3. Comparison HISlink and IMA Atlas based indicators

Table S2: Descriptive statistics and comparison with estimates from IMA Atlas

Indicators	**HISlink**	**IMA Atlas**
Percentage of the population with at least one preventive dental care in 2018	38.1	33.4%[a]
Percentage of the population aged 18 years and over with at least one preventive dental care in 2018*	40.1	-
Percentage of the population with a GMR in 2018	75.6%	75.5%[b]
Percentage of the population aged 15 years and over with a GMR in 2018*	78.5%	-
Percentage of the population with at least one prescription of antibiotics between 01/07/2018 and 30/06/2019	35.5%	-
Percentage of the population aged 15 years and over with at least one prescription of antibiotics between 01/07/2018 and 30/06/2019	35.8%	-
Percentage of the population aged 15 years and over with at least 90 DDD of prescribed antibiotics between 01/07/2018 and 30/06/2019	0.68	-
Volume of antibiotics (number of DDD) per 1000 persons per day between 01/07/2018 and 30/06/2019	24 DDD	20 DDD
Number of beneficiary with prescribed antibiotics per 1000 persons per day, population aged 15 years and over	0.98	0.98
Percentage of the adult population (18+ years) with prescribed antidepressants in 2018	12.97%	13.0%
Percentage of the adult population (18+ years) with at least 90 DDD of prescribed antidepressants in 2018	9.6%	-
Volume of antidepressants (number of DDD) per 1000 persons per day	97 DDD	77 DDD
Percentage of older population (65+ years) vaccinated against flu in 2018	57.2%	-
Breast cancer screening in women aged 50-69 in the past 2 years	62.1%	60.2%

**with valid information on HL*

Table S3: correlation between key variables

Variable				
Preventive dental care (n=6682)				
	Education	Income	Health literacy	Preventive dental care
Education	1			
Income	0.560**	1		
Health literacy	0.251**	0.133**	1	
Preventive dental care	0.318**	0.232**	0.054**	1
Global medical record (GMR, n=6878)				
	Education	Income	Health literacy	GMR
Education	1			
Income	0.565***	1		
Health literacy	0.249***	0.128***	1	
GMR	-0.147***	-0.060**	-0.029	1
Use of antibiotics				
	Education	Income	Health literacy	Use of antibiotics
Education	1			
Income	0.565***	1		
Health literacy	0.249***	0.128***	1	
Use of antibiotics	-0.073**	-0.050**	-0.036*	1
Vaccination against flu				
	Education	Income	Health literacy	Vaccination against flu
Education	1			
Income	0.514***	1		
Health literacy	0.390***	0.250***	1	
Vaccination against flu	-0.066	-0.024	-0.101**	1
Use of antidepressants				
	Education	Income	Health literacy	Use of antidepressants
Education	1			
Income	0.560***	1		
Health literacy	0.251***	0.133***	1	
Use of antidepressants	-0.119***	-0.207***	-0.151***	1
Breast cancer screening				
	Education	Income	Health literacy	Breast cancer screening
Education	1			
Income	0.472***	1		
Health literacy	0.197**	0.160**	1	
Breast cancer screening	0.231***	0.251***	0.047	1

*** P < 0.05; ***P < 0.0001; All P values are two-tailed*

Table S4: Results of mediator model[a] - association between HL(*Insufficient/limited level of HL" vs. "Sufficient level of HL*) and independent variables

	Odds Ratio (95% CI)					
	Preventive dental care	Global medical record	Use of antibiotics	Vaccination against flu	Use of antidepressants	Breast cancer screening
Educational attainment						
Lower secondary's degree or lower	2.19 (1.91-2.50)***	2.19 (1.92-2.50)***	2.19 (1.92-2.50)***	2.69 (2.13-3.38)***	2.19 (1.91-2.50)***	1.78 (1.32-2.39)**
Higher secondary's degree or higher	1	1	1	1	1	1
Household income category						
Lower household income	1.45 (1.29-1.62)***	1.43 (1.28-1.60)***	1.43 (1.28-1.60)***	1.77 (1.37-2.30)***	1.45 (1.29-1.62)***	1.54 (1.18-2.01)**
Higher household income	1	1	1	1	1	1

[a] *Adjusted by age and gender; ** p < 0.05; *** p < 0.0001.*

Table S5: Results of outcome model[a] - association between health outcomes, health literacy, education and household income

	Odds Ratio (95% CI)					
	Preventive dental care	Global medical record	Use of antibiotics	Vaccination against flu	Use of antidepressants	Breast cancer screening
Outcome model: association between health literacy, education attainment and health outcomes						
Health literacy						
Insufficient/limited level of HL	1.00 (0.89-1.12)	1.09 (0.96-1.25)	1.07 (0.95-1.21)	1.35 (1.01-1.79)**	1.62 (1.37-1.91)***	0.99 (0.74-1.32)
Sufficient level of HL	1	1	1	1	1	1
Educational attainment						
Lower secondary's degree or lower	0.47 (0.38-0.57)***	1.31 (1.04-1.65)**	1.09 (0.91-1.31)	1.12 (0.83-1.52)	1.08 (0.83-1.40)	0.59 (0.41-0.85)
Higher secondary's degree or higher	1	1	1	1	1	1
Educational attainment and HL interaction term	0.70 (0.51-0.95)**	0.92 (0.65-1.29)	1.07 (0.82-1.39)	0.67 (0.42-1.07)	0.91 (0.64-1.30)	0.76 (0.42-1.37)
Outcome model: association between health literacy, household income and health outcomes						
Health literacy						
Insufficient/limited level of HL	0.99 (0.84-1.15)	1.10 (0.92-1.32)	1.08 (0.92-1.27)	1.84 (1.17-2.89)**	1.50 (1.17-1.92)**	0.90 (0.59-1.39)
Sufficient level of HL	1	1	1	1	1	1
Household income category						
Lower household income	0.62 (0.54-0.71)***	0.94 (0.81-1.10)	1.03 (0.90-1.18)	1.06 (0.80-1.41)	1.49 (1.22-1.83)**	0.52 (0.38-0.71)***
Higher household income	1	1	1	1	1	1
Household income and HL interaction term	0.80 (0.64-1.01)	1.07 (0.83-1.40)	1.05 (0.84-1.32)	0.52 (0.31-0.89)	1.03 (0.75-1.43)	1.03 (0.59-1.79)

[a] *Adjusted by age and gender; ** p < 0.05; *** p < 0.0001*

4. Additional analysis

4.1. Physical activity (PA_1)

Table S6: Additional analysis: Physical activity †: Mediator model and Summary of effects for educational attainment and household income (n =)

	Odds Ratio[a] (95% CI)
Mediator model: *Insufficient/limited level of HL vs. Sufficient level of HL*	
Educational attainment	
Lower secondary's degree or lower	2.19 (1.91-2.50)***
Higher secondary's degree or higher	1
Household income category	
Lower household income	1.45 (1.29-1.62)***
Higher household income	1
Summary of effects of educational attainment	
Total Effect (TE)	0.51 (0.42-0.60)***
Natural direct effect (NDE)	0.57 (0.47-0.67)***
Natural indirect effect NIE)	0.90 (0.85-0.94)***
Percentage mediated (%)	12.1 (4.6 to 109.6)**
Summary of effects of household income	
Total Effect (TE)	0.66 (0.58-0.74)***
Natural direct effect (NDE)	0.68 (0.60-0.76)***
Natural indirect effect NIE)	0.97 (0.95-0.98)***
Percentage mediated (%)	6.6 (2.5 to 10.7)**

† *Spend at least 150 minutes per week in physical activities of at least moderate intensity;* [a] *Adjusted by age and gender; ** p < 0.05; *** p < 0.0001.*

4.2. Nutritional habits (NH_3)

Table S7: Additional analysis: Nutritional habits †: Mediator model and Summary of effects for educational attainment and household income (n =)

	Odds Ratio[a] (95% CI)
Mediator model: *Insufficient/limited level of HL vs. Sufficient level of HL*	
Educational attainment	
Lower secondary's degree or lower	2.19 (1.91-2.51)***
Higher secondary's degree or higher	1
Household income category	
Lower household income	1.44 (1.29-1.62)***
Higher household income	1
Summary of effects of educational attainment	
Total Effect (TE)	0.49 (0.38-0.59)***
Natural direct effect (NDE)	0.55 (0.42-0.67)***
Natural indirect effect NIE)	0.89 (0.83-0.95)**
Percentage mediated (%)	11.7 (3.1 to 20.4)**
Summary of effects of household income	
Total Effect (TE)	1.33 (1.11-1.55)**
Natural direct effect (NDE)	1.28 (1.07-1.48)**
Natural indirect effect NIE)	1.04 (1.02-1.07)**
Percentage mediated (%)	16.6 (5.7 to 27.4)**

† *Eating at least 5 portions fruits and vegetables daily;* [a] *Adjusted by age and gender; ** p < 0.05; *** p < 0.0001.*

5. Sensitivity analysis

5.1. Use of antidepressants (90 DDD threshold)

Table S8: Association between HL and independents variables (mediator model) and mediation effects of HL in the relationship between use of antidepressants and independent variables (summary of effects). Use of antidepressants is defined using the 90 DDD threshold per year

	Odds Ratio[a] (95% CI)
Mediator model: *Insufficient/limited level of HL vs. Sufficient level of HL*	
Educational attainment	
Lower secondary's degree or lower	2.19 (1.91-2.50)***
Higher secondary's degree or higher	1
Household income category	
Lower household income	1.45 (1.29-1.62)***
Higher household income	1
Summary of effects of educational attainment	
Total Effect (TE)	1.00 (0.79-1.21)
Natural direct effect (NDE)	0.94 (0.74-1.15)
Natural indirect effect NIE)	1.06 (0.99-1.14)
Percentage mediated (%)	3008 (-325412 to 331427)
Summary of effects of household income	
Total Effect (TE)	1.45 (1.19-1.72)**
Natural direct effect (NDE)	1.40 (1.14-1.65)**
Natural indirect effect NIE)	1.04 (1.02-1.07)**
Percentage mediated (%)	12.7 (4.0 to 21.3)**

*. [a] Adjusted by age and gender; ** p < 0.05; *** p < 0.0001.*

5.2. Use of antidepressants adjusted for psychological distress

Table S9: Association between HL and independents variables (mediator model) and mediation effects of HL in the relationship between use of antidepressants and independent variables (summary of effects). Use of antidepressants adjusted for psychological distress

	Odds Ratio[a] (95% CI)
Mediator model: *Insufficient/limited level of HL vs. Sufficient level of HL*	
Educational attainment	
Lower secondary's degree or lower	2.14 (1.86-2.46)***
Higher secondary's degree or higher	1
Household income category	
Lower household income	1.34 (1.19-1.50)***
Higher household income	1
Summary of effects of educational attainment	
Total Effect (TE)	0.98 (0.79-1.17)
Natural direct effect (NDE)	0.94 (0.75-1.14)
Natural indirect effect NIE)	1.04 (0.97-1.10)
Percentage mediated (%)	-162.6 (-1665 to 1340)
Summary of effects of household income	
Total Effect (TE)	1.37 (1.14-1.60)**
Natural direct effect (NDE)	1.35 (1.12-1.57)**
Natural indirect effect NIE)	1.02 (1.00-1.03)
Percentage mediated (%)	5.5 (-0.8 to 11.9)

*. [a] Adjusted by age, gender and psychological distress; ** p < 0.05; *** p < 0.0001.*

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CONTACT
>contactperson • T+32 2 >xxx xx xx • >first name.last name@sciensano.be

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info@sciensano.be • www.sciensano.be

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